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"PROGNOSIS IN SARCOMA OF THE UVEA"*

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Prefatory Note—In Acknowledgement

The subject of this thesis is so difficult, that it would have been impossible of accomplishment without the help of a pathologist and a well-equipped laboratory. This help was forthcoming from Mr. C. Dee Shapland, the then pathologist and now an Honorary Surgeon in the Royal London Ophthalmic Hospital (Moorfields) London, E.C.1. He did everything possible to help me by giving me the free use of his laboratory, the benefit of his guidance, and throughout he has taken very keen interest in the progress of this work. Richard Sutton, known to one and all as "Dick," the laboratory assistant at Moorfields did all that was required of him to help me to prepare the microscopic sections.

I have also to thank Mr. Goulden, the Dean, and Miss Lloyd-Jones, the Secretary of the Medical School of Moorfields, for giving me permission to carry out this work at the hospital, Mr. Ridley, the Registrar, and his secretary, Miss Paddington, supplied me with various lists, figures, and other particulars required by me, and also for permitting access to the records of the various patients.

* This was the thesis submitted for the degree of M.D. of Glasgow University, and permission for its publication has been obtained.

I have to thank all the Honorary Surgeons of Moorfields for giving me permission to make use of their records and clinical notes on all the patients used for this investigation.

And lastly, my acknowledgements are due to the authors of all the papers and books which I have quoted in the text, a complete list of these will be found on succeeding pages.

I.—Introduction and Plan of This Work

DURING recent years a considerable amount of literature has been written regarding the prognosis in sarcoma of the uvea. Several statistics have been published regarding the incidence of this disease, the number of deaths from metastases, the time interval between the occurrence of the disease and the time of death. A list of all the important papers and references on the subject is given in the bibliography of this paper, and on going through all of them the work of E. von Hippel[17 18 19 20], Callander[2 3], and Callander and Wilder[4 35] merits special attention, E. von Hippel's for his very careful statistics about the cases which he has been following for a number of years, some of them for over 20 years, which he has been checking and re-checking time and again, Callander's, and Callander and Wilder's for suggesting new ways of evaluating the prognosis in sarcoma of the uvea.

Among the publications of these three authors, three new ways of arriving at the prognosis in this disease are suggested, and this paper is written to investigate the claims of two of them.

The three methods are:—

(1)[4 35] ***Prognostic significance of the quantity of reticulin found in a section of the growth after enucleation.***—Callander and Wilder first published the details of this method in the ***Amer. Jl. of Cancer***, October, 1935. They showed how the reticulin fibre distribution not only varies in different growths, but also in different areas of the same growth. H. and E. staining gives no indication regarding the quantity of reticulin or correspondence to presence of its fibres. Special silver staining methods are required to demonstrate its presence. And they showed that the prognosis becomes progressively worse as the quantity of reticulin becomes less. They of course clearly state that this method by itself is not reliable, the original method described by Callander[2] of cell typing still holds good, but a very much more accurate prognosis can be given if this method is used as an aid to cell typing.

The details of this method will be discussed in a later chapter.

(2) ***Prognosis as judged by histological cell-types.***—Callander[2 3] describes how each sarcoma can be classified in one of the following four groups according to the type of cell found in it. They are: 1. Spindle cell (Sub-type A or B); 2. Fascicular type; 3. Epithelioid type; 4. Mixed-cell types, and he goes on to describe that

each particular type differs in malignancy: whereas spindle types are comparatively benign, the others become progressively more malignant in the order named above. They have published statistics from a very large number of cases in support of the above. Other authors (Terry and Johns[34], McKee[23]) have also published their cases supporting the above classification with some variations. The details will be discussed in a later chapter.

(3) E. von Hippel[20] has recently published a new method of determining the prognosis in sarcoma *based on the method of Klein of Ludwigshafen.*

This method is based on the fact that the serum of non-carcinomatous individuals is capable of destroying the cells of malignant tumours, while that of sarcomatous or carcinomatous individuals is not. Therefore every case of sarcoma should be tested with this reaction before enucleation. The positive reaction which is to be expected may become negative after the operation. If this change takes place in about two months after the operation, the prognosis should be considered favourable, but if the reaction still remains positive for three months or later after the operation, an enquiry will probably show that the patient has died from metastases. The test should be repeated at intervals, and the patient should be kept under observation for at least ten years. Further research and co-operation between many workers is required before it can be stated that this method is of clinical use in determining the prognosis in uveal sarcoma.

In this paper I have endeavoured to investigate the clinical applicability of the first two methods, that is "Is it possible by the reticulin content of a growth or by the type of cell found in a growth to give an accurate prognosis after enucleation as to whether the patient will remain free from, or succumb to metastases." The results given in subsequent chapters speak for themselves.

I do not propose to follow the third (E. von Hippel's method) any further, I have only mentioned it for the sake of pointing out all recent work on the subject.

During the years 1930 and 1935, both inclusive, that is for a period of six years, 100 patients suffering from sarcoma of the uvea were admitted into the Royal London Ophthalmic Hospital (Moorfields). For the purposes of this investigation I chose the cases from the above six years 1930 to 1935 for the following reasons:—

1. In the hospital class of patients considerable difficulty is experienced in tracing the patients after the lapse of a long time, and this period is not too long, even in this period as I shall presently show, a certain number of cases could not be traced.

2. The majority of cases in this series were operated upon more than five years ago, and none less than three years ago. So

sufficient time has elapsed to conclude that the majority of patients who have escaped metastases so far, have in all probability escaped from them permanently.

3. This period has furnished 100 cases, which number is large enough to make the results of some value.

From these 100 cases, for some reason or the other, four patients were not treated at Moorfields, and in the case of one private patient no attempt was made to trace him as his records were not available, so that left me with 95 cases on which to carry out my investigations.

Unfortunately, from the 95 eyes that were excised, 23 blocks were missing, so there were only 72 blocks from which the investigations on the significance of argyrophile fibres (reticulin) in determining the prognosis in sarcoma of the uvea were made. The sections of these 72 blocks were prepared and stained with special silver staining methods described elsewhere, and then they were grouped in different categories according to the amount of reticulin found in each section. Then the prognosis, solely from reticulin content, as well as in conjunction with histological types was judged, and the results are recorded in a later chapter.

Side by side the H. and E. section of each patient was examined and classified according to Callander's[2] classification, that is whether it was purely spindle cell sub-type A or B, fascicular, epithelioid, or mixed cell growth; if last which was the predominant type of cell. In a certain number of slides, some difficulty was experienced in grouping them in their respective classes, the reasons for these difficulties and the way they were overcome, are described elsewhere. The prognosis in each case was judged according to the type of cell found in each growth (in case of mixed tumours by the predominating cell). From the 95 eyes removed at Moorfields, three H. and E. sections were missing, so only 92 slides could be examined, and the results as found are recorded in the chapter dealing with the subject.

After the preparation and classification of all these sections, an attempt to get in touch with the patients was made. The following procedure was adopted.

A questionnaire with a stamped addressed envelope was sent out: it asked for the following information:—

1. Their general health since the operation.
2. The condition of the socket.
3. If they have had any serious illness since the operation, if so the diagnosis, and the name of the hospital or the private practitioner who attended them.
4. Change of address if any.

No further action was taken on the replies which showed that the patients were alive and well, but in the cases where the relatives of the deceased wrote that the patient had died, a further letter

asking them the exact cause of death if known to them, the date of death, and the name of the doctor or the hospital where the patient had received medical assistance for his last illness, was sent out. Then if necessary an enquiry was made from the patient's doctor or the hospital in which the patient had died to find out the exact cause of death.

In several cases there was no reply in spite of weekly reminders, and also several letters were returned by the Post Office as undelivered, an attempt was made in all these cases to get in touch with them by calling at the addresses as shown in the books of the hospital. Enquiries were made from the present tenants of the addresses, the neighbours, or the local doctors, and if necessary, as it was in many cases, calls were made at the new addresses received from these sources, thereby the whereabouts of many patients were traced. This last was a very tedious and laborious work, and it took two months of daily running about to accomplish.

In spite of all these efforts, in a certain number of cases, as is inevitable in an investigation of this character, no trace of the patient could be found, so these cases are recorded as patients lost or untraced. The exact number of these cases is ten. The results of all these investigations are described elsewhere; here it is sufficient to mention that the 95 cases which I attempted to trace, I found:—

1.	Patients alive		51
2.	Patients dead of (i) Metastases	27	
	(ii) Other causes ...	4	
	(iii) Unknown cause ...	3	
	Total dead		34
3.	Patients lost or untraced		10
	TOTAL ...		95

I have also included in this paper a chapter on statistics, to show the incidence of sarcoma of the uvea to all eye diseases, to out-patients, to in-patients, incidence as regards age and sex are concerned, and the various parts of the uvea affected.

A warning here about the time limit in judging the prognosis in sarcoma of the uvea, this question is a very vexed one. So far as published records go there does not seem to be any time limit after which secondary growths do not take place. At present most of the authorities are agreed that if metastases have not taken place within five years of enucleation, in a large majority of cases they probably will not take place at all. However, there are so many cases reported where secondary growths have taken place after five years, and a few after ten years, that von Hippel's[17] conclusion that "there is no limit after which a certain cure can be assumed"

seems to be justified. On the other hand, the number of patients who develop metastases after five years is so small, that if a patient has remained free for so long, he may within reason be expected to remain free from them for all time. So whenever any conclusions on the prognosis in this disease are judged, this fact should always be borne in mind. So wherever required I have divided the list of my cases living in my tables in two categories.

1. Those who are alive for more than five years.
2. Those who are alive from three to five years.

During the follow-up of these patients, I discovered that one of the patients, although alive was suffering from metastases: she has been classed among the patients dead of secondary growths in all the tables.

II.—Reticulin

In the intra-cellular elements of connective tissue, three kinds of fibres are found:—i. collagen fibres; ii. elastin fibres, and iii. reticulin fibres. It is with the study of the last named that we are concerned, that is with the quantity of reticulin found in a given section of the sarcoma of the eyeball, and whether a definite prognosis can be given from the quantity of reticulin valuated.

1. RETICULIN STAINING

Reticulin is not demonstrable by ordinary stains, it only takes up silver stains, hence its fibres are called argyrophile fibres. With silver stains its fibres appear as prominently black branching extensively against brownish stains of the tumour cells and their nuclei.

Several silver staining methods have been described such as Ranson-Ramon-Y-Cajal, Bielschowsky and other methods, Foot's method for general laboratory purposes as modified by Wilder is the one used by me for staining my sections[11 12 13 14 15 35]. This method has made the process a short one without the loss of detail. For the sake of brevity and also because of the fact that considerable discussion on staining methods is out of place, I shall only describe the method with which all my sections were stained, that is the one described by H. C. Wilder in the *Amer. Jl. of Path.*, Sept., 1935. This method is a modification of Foot's method, and is simple, quick, and efficient. It stains the finest reticulin fibres with great precision, no heat is required. Prior to exposure to ammoniacal silver (Foot's silver di-amino-hydroxide) sections are sensitised with uranium nitrate solution.

The exact technique is as follows:—

1. *Sections* are made in the usual way, that is paraffin, celloidin, or frozen. Then sections are cut the required thickness 4 to 30 microns thick. Thicker sections give a better idea of density, the thickness used by me was about 18 microns.

2. *Pre-treatment.* Place the section in 0·25 per cent. potassium permanganate solution for 30 minutes in the sun, or at a temperature of 39° for a few minutes. Ten per cent. phosphomolybdic acid for one minute may be used instead. Rinse in distilled water, and place the section in hydrobromic acid (Merck's concentrated 34 per cent. one part, and distilled water three parts) for one minute.

Hydrobromic acid may be omitted if phosphomolybdic acid is used.

3. *Sensitization.* Wash in tap water, then in distilled water, and dip the section in one per cent. uranium nitrate (sodium free) for five seconds or less.

4. *Silver impregnation.* Wash in distilled water for 10-20 seconds and place it in silver di-amino-hydroxide for one minute.

Silver di-amino-hydroxide is prepared as follows:—To 5 c.c. of 10·2 per cent. silver nitrate solution add ammonium hydroxide drop by drop until the precipitate which forms is just dissolved. To this add 5 c.c. of 3·1 per cent. sodium hydroxide and just dissolve the resulting precipitate with a few drops of ammonium hydroxide. Then add distilled water to make the solution up to 50 c.c.

5. *Reduction.* Dip quickly in 95 per cent. alcohol, and reduce for one minute in a solution consisting of distilled water 50 c.c., 40 per cent. neutral formalin (neutralised by magnesium carbonate) ½ c.c., and uranium nitrate 1 per cent. 1·5 c.c.

6. *Toning.* Wash in distilled water, and place the section in 0·2 per cent. (1/500) gold chloride (Merck's) for one minute. Rinse in distilled water and place the section in 5 per cent. sodium thiosulphate for 1-2 minutes.

7. *Counterstaining.* Wash in tap water, and if required sections can be counterstained with haematoxylin, or haemalum and eosin.

The sections in this series were not counterstained.

8. *Mounting.* Dehydrate with: i. methylated spirit; ii. carbol xylol, and mount the sections in canada balsam.

Alcohol up to 95 per cent. may be used but never absolute alcohol.

Note.—Solutions can be used repeatedly for several days, they keep well without disintegrating if kept in amber-coloured stoppered bottles indefinitely.

Summary. Bromuration as pretreatment is better than pyridine treatment for reticulin staining. In this method reticulin is shown as sharply black. Apart from soaking the section in potassium permanganate solution, because of the sensitization with uranium nitrate, the whole process can be carried out in a very short time, leaving the section in silver nitrate solution for days is not required.

III.—Reticulin Content of a Growth

Reticulin fibre content varies in different growths from complete absence to dense intracellular network, any gradation between

these two extremes is met with. It may also vary in different parts of the same growth, or even in different parts of one section. For accurate assessment several sections from different parts of a growth should be prepared, but for the purposes of this work one complete microscopic section of the growth was used as a basis for classification. In several cases other sections were prepared, but no marked change was recorded, but one complete section gives approximate valuation only.

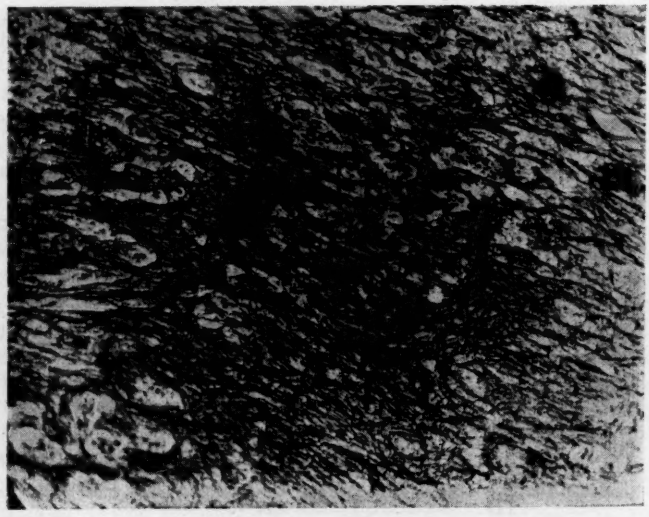
The sections so prepared and examined are divided into three groups:—

Group 1. In which large quantities of reticulin fibres were found throughout the growth.

Group 2. In which in some areas reticulin fibres were in large quantity, in others small or totally absent.

Group 3. In which reticulin fibres were totally absent except at the periphery of the growth, or at the periphery of lobulated masses of cells, but they did not penetrate between individual cells.

Group 1.—The slides classified under this group not only showed large quantities of reticulin fibres between lobules of cells, but their branches penetrated between individual cells of the growth; some idea of the quantity of reticulin can perhaps be obtained from the following microphotographs.



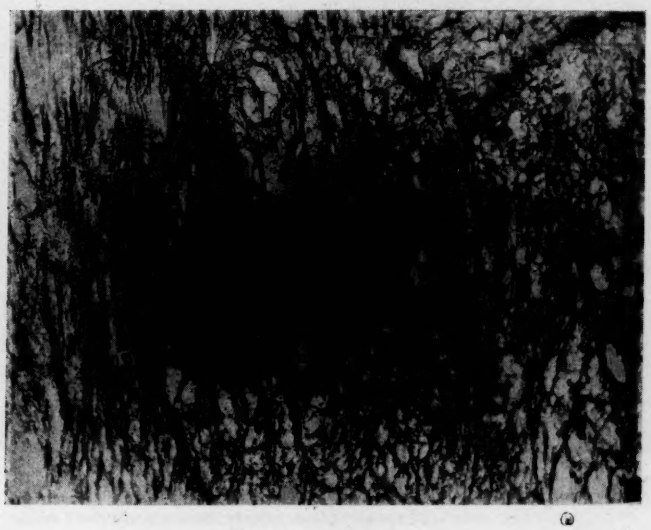
MICROPHOTOGRAPH 1.

Showing dense reticulin network. Magnification 110.

MICROPHOTOGRAPH 2.

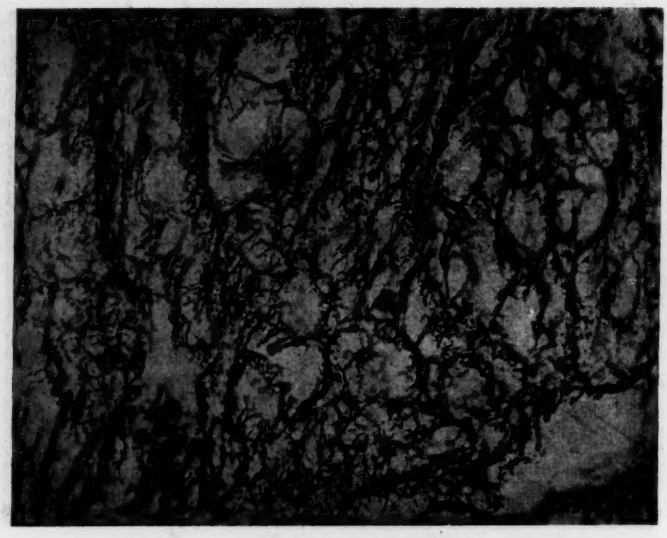
Same as 1, but under high power. Magnification 340.

In the photograph No. 2 it will be seen that the reticulin fibres are branching extensively, and they are penetrating between individual cells. In this section very large quantites of fibres were met with.



MICROPHOTOGRAPH 3

Showing dense reticulin fibre network, but not so dense as in photo No. 1. Low power, 110.

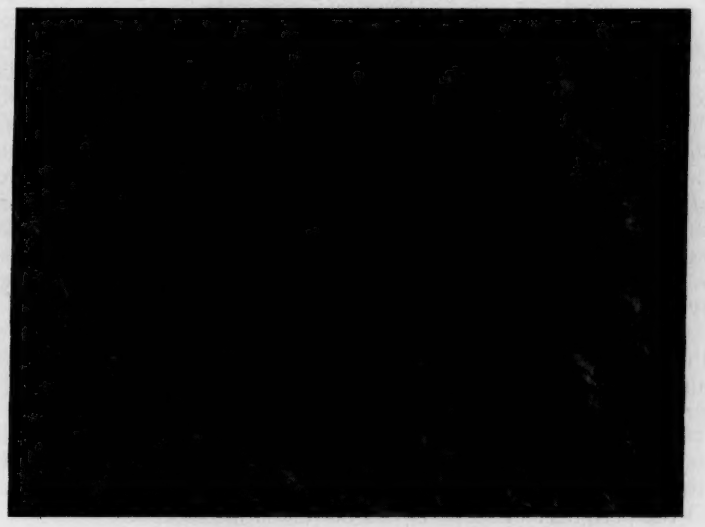


MICROPHOTOGRAPH 4.

Same as No. 3, but under high power. Note extensive branching and fibres penetrating between individual tumour cells. Magnification 340.

MICROPHOTOGRAPH 5.

Showing dense reticulin fibre network. The fibres in this growth are very fine, and they are branching extensively, at one place their origin from blood-vessels is noticed. Low power 110.



MICROPHOTOGRAPH 6.

Same as No. 5 but under high power. Very fine fibres between each cell are seen. The fibres are in focus, the cells are not, but their nuclei can be recognised as dots: these are nucleoli. High power 340.

MICROPHOTOGRAPH 7.

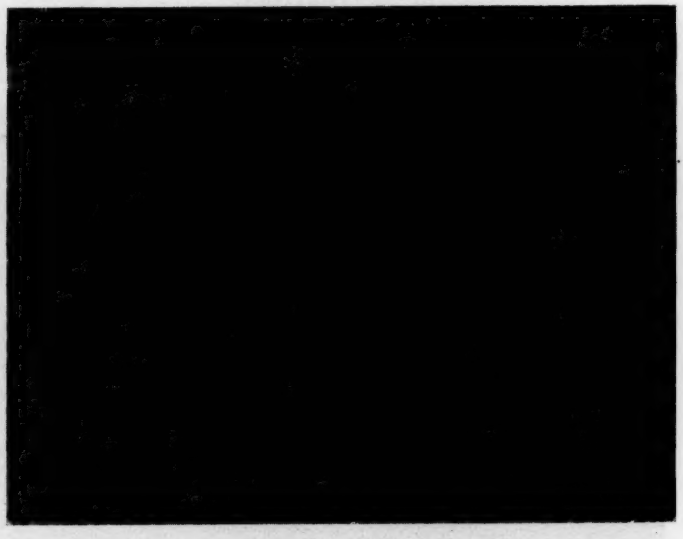
The reticulin network is not so dense as in preceding ones, the fibres are branching extensively, in some clumps of cells the fibres have penetrated between individual cells, in the others they have not. Note the origin of the fibres from blood-vessels. Magnification 340.

The above are some of the pictures to illustrate the type of growth in which large quantites of reticulin are found.

This type of section is specially liable to be found in the spindle cell variety. Spindle cells show fibre formation more extensively than other varieties of sarcoma cells. In my series 20 sections showed this type; that is that they belonged to Group 1. From this statement it must not be assumed that large quantities of reticulin are only found in the spindle-cell variety, because they are found in other types of sections also. In this series of 20 cases belonging to this group (Group 1), 12 are from spindle-cell variety, three fascicular, three epithelioid, and two from mixed-cell type.

The main criterion by which a section is placed in this group is the fact that reticulin is not only found in large quantities, but it also penetrates between individual cells almost throughout the growth.

Group 2.—In this group reticulin is found in some parts of the section in small or large quantities, and is absent in other parts. For the purposes of classification under this group, reticulin found at the periphery of sections was not taken into account.



MICROPHOTOGRAPH 8.

It will be noticed that reticulin is present round clumps of cells, although it is branching, but the branches are not abundant, and their extension between individual cells is not marked. To get an idea that this slide is from the mixed variety, *i.e.* Group II, see photos 9 and 10.

This group is further divided into three sub-groups:—

(*a*) In which reticulin is found in the major part of the growth, that is if it can be definitely stated that it is present in quantities in more than half of the growth.

(*b*) In which it is difficult to say whether the areas with reticulin are more or less than the areas without reticulin. That is that reticulin is present in about half the growth.

(*c*) In this group areas without reticulin preponderate over the areas with reticulin, that is reticulin is only present in less than half the section looked at.

To illustrate the type of section which is classified in this group.

Out of a total of 72 sections examined by me, a very large number belonged to this group, to be exact, 45; and out of these 16 belonged to sub-group A, 10 to B, and 19 to C.

Again it is noticed that the spindle-cell variety shows greater tendency to fibre formation than other varieties, in 16 sub-group (*a*) cases, 8 are spindle-celled, 1 fascicular, 1 epithelioid, 5 mixed-celled cases, and 1 not classified. In sub-group (*b*), 1 spindle-celled, 4 epithelioid, and 5 mixed-celled, a total of 10. Sub-group (*c*), 3 spindle-celled, 3 fascicular, 5 epithelioid, and 8 mixed-celled type, a total of 19 cases.

MICROPHOTOGRAPH 9.

This is a silver stained section to show almost complete absence of reticulin fibres, a few strands here and there can be recognised. This photograph is from the same slide as No. 8, one part of the section contained reticulin, the other did not. Low power 110.

Group 3.—In this group reticulin is almost completely absent except at the periphery of the growth, a few strands round the blood-vessels may be seen, but that is about all.

MICROPHOTOGRAPH 10.

Same as No. 9 but under high power to show total absence of reticulin fibres. Magnification 340.

In this series of 72 sections, only 7 belonged to this group, 1 spindle-celled, 1 fascicular, and 5 epithelioid, none from mixed-celled cases.

Summary

Reticulin Groups.					Total No. Slides.
Group 1.	(+ + + +)	...	...	...	20
Group 2. A.	(+ + + —)	...	...	...	16
B.	(+ + — —)	...	...	...	10
C.	(+ — — —)	...	...	...	19
Group 3.	(— — — —)	...	...	...	7
		TOTAL		...	72

IV.—Reticulin Content and Prognosis in Sarcoma of the Uvea

Callander and Wilder in the *Amer. Jl. of Cancer*[4 36] first published the prognostic significance of argyrophile fibres, and they came to the conclusion that the presence of reticulin was of very good prognostic significance. They recorded :—

No deaths in Group 1.
22 per cent. in Group 2 A
76 per cent. in Group 2 B } 68 per cent.
87 per cent. in Group 2 C
100 per cent. in Group 3.

They came to the conclusion that if in addition to the cell type classification, reticulin classification is also used, a very much more accurate prognosis can be given, and they stated that growths can be further sub-divided in groups of relative malignancy, and that deaths in spindle-celled groups can be explained by the presence of areas containing no argyrophile fibres.

In the main during this investigation, my findings are more or less the same as theirs except that there is a difference from the percentages they have recorded, both as regards the incidence of various types and the number of deaths in each group. There is no doubt that in the cases which are full of reticulin, whether they belonged to spindle-cell type or other groups, the prognosis is good, and it became progressively worse as the quantity of reticulin decreased.

To analyse these findings in greater detail, out of the 100 cases which reported at Moorfields as suffering from sarcoma of the uvea during the years 1930 and 1935 both inclusive, 51 are alive, 10 could not be traced, 27 died from metastases, 4 died from other causes, 3 died from unknown cause, in case of 4 the eye was not excised at Moorfields, and in the case of one private patient no attempt was made to trace him.

Alive		51
Patients untraced		10
Deaths: i. Due to metastases		27
ii. Other causes		4
iii. Unknown causes		3
Total ...		95
Eyes not excised		4
Not attempted to trace		1
Total ...		5
Total No. of cases		100

Cases Alive.—The cases which are alive are divided by me into two groups, one which are alive for more than five years, that is the ones which were operated upon during the years 1930 and 1933, and the second group which are alive from three to five years, that is the ones which were operated upon during 1934 and 1935. In the first group there are 29 cases, and in the second there are 22, the reticulin content of these cases is as follows:—

Reticulin Groups		Cases alive over 5 years	Cases alive 3 to 5 years	Total
Group 1.	(+ + + +)	12	6	18
Group 2. A.	(+ + + —)	7	4	11
B.	(+ + — —)	3	4	7
C.	(+ — — —)	1	1	2
Group 3.	(— — — —)	—	1	1
Eyes missing		6	6	12
Total		29	22	51

It will be noticed from this table that out of the 39 cases alive whose eyes have been sectioned and examined (there are 12 missing), 29 belong to group 1 and group 2A, while only 10 belong to other groups, it will also be noticed that there is only one patient alive from group 3, and that case was operated upon in 1935, that is only three years ago. It is also seen from above that the number of cases alive falls as we descend in the reticulin content scale.

Deaths and reticulin.—I have recorded above that out of the 85 cases traced, 27 died from metastases, 4 from other causes, and 3 from unknown cause. The reticulin analysis of these cases is as under :—

Reticulin Groups		Deaths: Metastases	Deaths: Other cause	Deaths: Unknown cause	Total
Group 1.	(+ + + +)	—	—	1	1
Group 2. A.	(+ + + —)	3	—	—	3
B.	(+ + — —)	3	—	—	3
C.	(+ — — —)	14	1	—	15
Group 3.	(— — — —)	3	2	—	5
Eyes missing		4	1	2	7
Total		27	4	3	34

Here again it will be noticed that there is not a single death from group 1 which can be definitely ascribed to secondary growths; despite repeated enquiries the cause of one death recorded in this group could not be ascertained. The majority of deaths from metastases are found in group 2C, *i.e.*, those in which the major portion of the growth did not contain reticulin, and as the amount of reticulin diminishes the chances of secondary growths taking place increase.

It is mentioned above that out of the 95 eyes excised at the Royal London Ophthalmic Hospital (Moorfields) during the years 1930 to 1935, 23 were missing, and therefore I was able to prepare the sections of 72 eyes only, and these were stained with silver stains described above, and their reticulin content and the results of follow-up are as follows :—

Reticulin Groups	Total	Cases Alive				Cases Dead					Untraced
		Over 5 years	3 to 5 years	Total alive	% alive	Metastases	Unknown cause	Other causes	Total deaths	% deaths due to metastases	
Group 1. (+ + + +) ...	20	12	6	18	90	—	1	—	1	5*	1
Group 2. A. (+ + + −) ...	16	7	4	11	69	3	—	—	3	19	2
B. (+ + − −) ...	10	3	4	7	70	3	—	—	3	30	—
C. (+ − − −) ...	19	1	1	2	10	14	—	1	15	74	2
Group 3. (− − − −) ...	7	—	1	1	14	3	—	2	5	43‡	1
Total ...	72	23	16	39	54	23	1	3	27	33	6

*Deaths due to unknown cause are included in the percentage deaths due to metastases, as it is assumed that they have died of secondary growths.

‡Owing to deaths under 'Other causes' and one untraced patient, this percentage is lower than it should have been.

It will be noticed that the percentage of patients alive falls as we descend in the reticulin scale, and the percentage of patients dead of metastases increases as we descend in the reticulin scale. I have mentioned above that the patient alive in group 3 was operated upon as recently as in 1935, that is that he is alive just for three years, and this fact should be taken into account when judging the percentages of cases alive in that group. It will be interesting to follow that patient after a year or so.

For comparison, the percentages as recorded by Callander and Wilder as regards the deaths from metastases are as follows:—

	Callandar and Wilder Per cent.	Present Series Per cent.
Group 1. ...	None	5*
Group 2A. ...	22	12
B. ...	76	30
C. ...	87	74
Group 3. ...	100	43‡

*See note below the table above.
‡See note below the table above.

Differences in the above percentages can probably be explained by the fact that the figures of the above authors are worked out

from the cases which they have followed for five years or longer, and they have not included in their total the cases untraced, or those dead from other causes.

Conclusions.—From the preceding tables and description, there is no doubt about the fact that a definite prognostic significance can be attached to the quantity of reticulin found in a growth, the more the reticulin the better the prognosis, and if a case belongs to group 1, then a good prognosis can be given with reasonable certainty, on the other hand, if the slide belongs to group 3 or to group 2C, a bad prognosis can be given with equal certainty, in that case it can be assumed that the patient will probably succumb to metastases.

This question will be discussed in greater detail after description of the 'cell type classification.'

Summary

	Alive	Dead	Untraced	Total
Group 1.	18	1	1	20
Group 2A.	11	3	2	16
B.	7	3	—	10
C.	2	15	2	19
Group 3.	1	5	1	7
Total	39	27	6	72

V.—Relation between type of cell found in a growth and reticulin content

I have already indicated above that spindle-cell growths show greater tendency to fibre formation than other type of growths, although this is not invariably the case, as there are cases in this series belonging to the spindle-celled group yet showing total absence of reticulin, and there are also cases of fascicular, epithelioid, and mixed-celled variety, which belong to group 1 of reticulin classification. In studying the relation of reticulin and the cell type found, the following figures were arrived at:—

Reticulin groups	Spindle A and B	Fascicular	Epithelioid	Mixed Growths	Total
Group 1.					
(+ + + +)	12	3	3	2	20
Group 2A.					
A. (+ + + —)	8	1	1	5	16*
B. (+ + — —)	1	—	4	5	10
C. (+ — — —)	3	3	5	8	19
Group 3.					
(— — — —)	1	1	5	—	7
Total	25	8	18	20+1*	72

*Includes one case not included in cell classification.

From the above table it is obvious that beyond the fact that spindle-cell type growths in most cases show a greater quantity of reticulin, and epithelioid growths usually show a small quantity of reticulin, no other relation can be established. But what is important is that malignant growths like epithelioid when they do show a large quantity of reticulin, become less malignant. This aspect will be discussed in the next chapter.

VI.—Classification of sarcoma of the uvea by histological types

Callander in describing the histological types in *Transactions of the American Academy of Ophthalmology*, 1931[2] states that all malignant melanomas of the uvea can be grouped histologically in four definite types. He describes the following :—

1. Spindle-cell type.
2. Fascicular type.
3. Epithelioid type.
4. Mixed-cell type.

1. *Spindle-cell type.*—This is the most commonly found type of cell, either solely by itself or in mixed tumours, the cells are arranged in sheets, whorls, or irregularly, cells are long, spindle-shaped, and the ends appear to terminate in fibres, thereby resembling fibroblasts. Cells are closely packed, and they have a long oval nucleus.

According to the type of nucleus the purely spindle-cell growths are further divided in two sub-groups.

Sub-Type A.—In which the nucleus has a delicate reticular structure, and the nucleolus is not well defined, these growths contain a fair amount of pigmentation. This type is found in choroidal growths only.

Sub-Type B.—In these there is a sharply defined deeply stained small round nucleolus near the centre of the nucleus in coarse nuclear network. These tumours are generally lightly pigmented, and many of them are white tumours or leuco-sarcomas. This type is often found in mixed-celled tumours, and ingrowths of choroid and ciliary body.

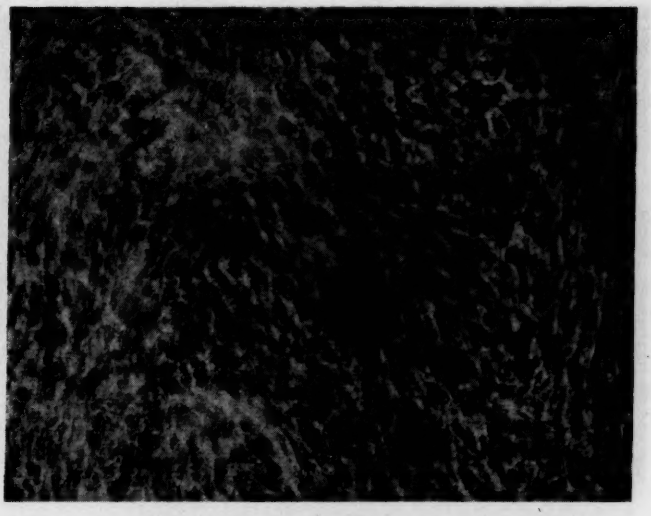
2. *Fascicular type.*—This type is not distinguished so much from the shape of the nucleus, or the shape of the cell, as from the arrangement of the cells. The majority of the cells are arranged in columns or fasciculi, the long axis of cells is at right angles to that of the column, and they radiate out in a palisade manner from a lymphatic or blood-vessel, in cross section they give the appearance of a pseudo-rosette. The cells are elongated and fibre-like, there is an oval nucleus with a prominent nucleolus resembling that of spindle-cell Sub-Type B.

MICROPHOTOGRAPH 11.

Showing a pure spindle-cell growth, this particular section belongs to Sub-Type A. Magnification 110.

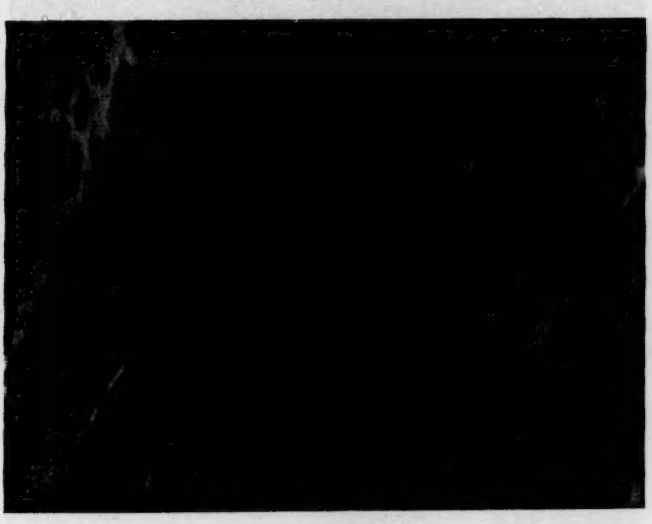
MICROPHOTOGRAPH 12.

Showing Sub-Type A cells, no distinct nucleolus can be recognised. Magnification 340.



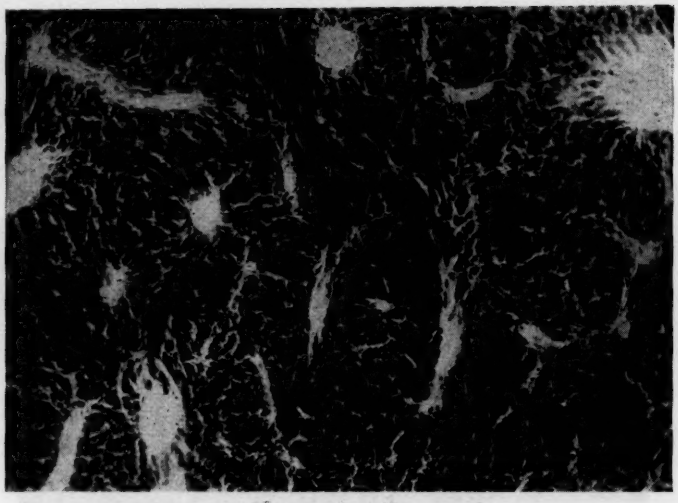
MICROPHOTOGRAPH 13.

Showing spindle-cell Sub-Type B, this photograph is from a mixed-cell growth, but spindle cells with prominent nucleoli can be recognised. Magnification 340.



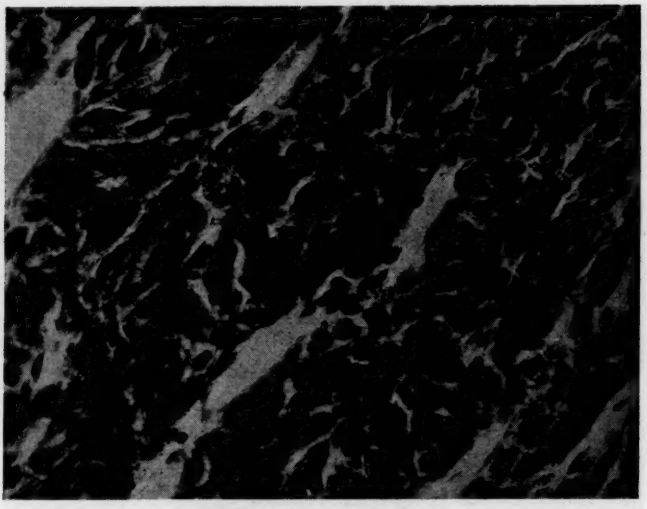
MICROPHOTOGRAPH 14.

Also showing spindle-cell Sub-Type B. Prominent nucleolus can be seen. Magnification 340.



MICROPHOTOGRAPH 15.

Showing a fascicular type of growth. Note the arrangement of the cells radiating out from blood vessels. Magnification 110.

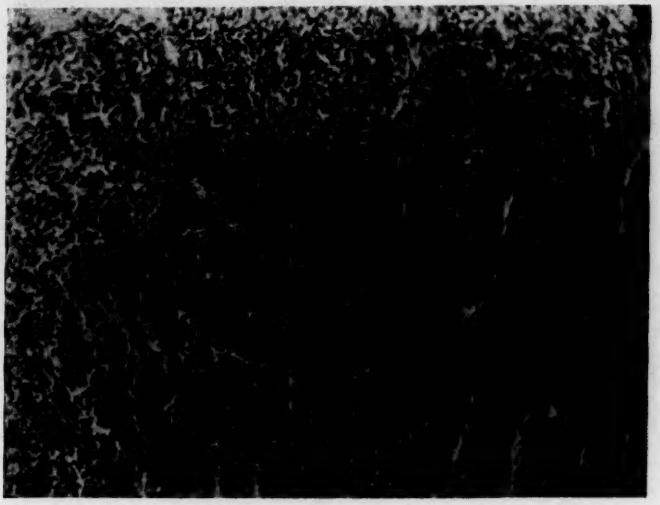


MICROPHOTOGRAPH 16.

Same as No. 15 showing fascicular type of cells under high power. Magnification 340.

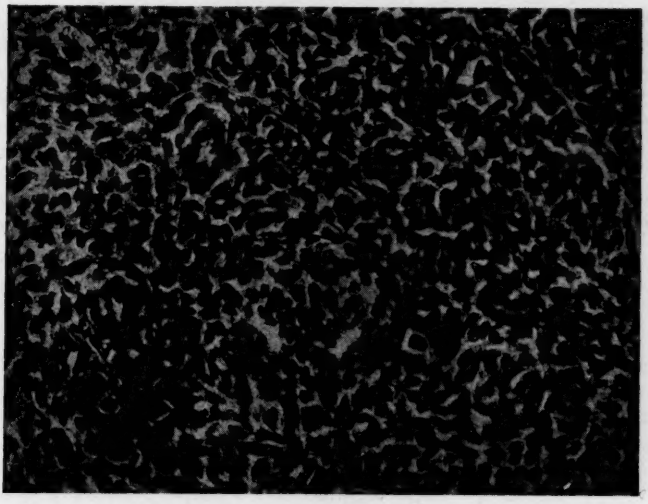
3. *Epithelioid type.*—The cells are polygonal, they are relatively large, although their size varies considerably in different growths.

The cells have a large nucleus, round or oval, with one or two distinct nucleoli. This type of cell is also commonly found in mixed-cell growths.



MICROPHOTOGRAPH 17.

Showing epithelioid type of growth under low power. Magnification 110.



MICROPHOTOGRAPH 18.

Showing epithelioid growth under high power. Magnification 340.

MICROPHOTOGRAPH 19.

Showing epithelioid growth under high power. The cells in this growth are very large ones. Compare this size with the size of the cells in photo No. 18. Magnification 340.

4. *Mixed-cell type.*—These are the commonest melanotic tumours of the eye, there is an irregular mixture of spindle and epithelioid cells, with an occasional area of fascicular type. Commonly there are small areas composed entirely of one or other cell type, but sometimes various types of cells are mixed in close association. Usually these growths are heavily pigmented.

ii.—*The incidence of various types.*

G. R. Callander in the *Transactions of the American Academy of Ophthalmology and Laryngology*[3] gives the following figures from 237 cases.

Spindle-cell	Sub-Type A ...	31
	Sub-Type B ...	54
Epithelioid	... ...	17
Fascicular	... ...	12
Mixed ...	... ...	123
	Total ...	237

Terry and Johns[34] from a series of 65 cases record almost similar incidence, their exact figures being :—

Spindle-cell Sub-Type A ...	6
Sub-Type B ...	12
Epithelioid	8
Fascicular	8
Mixed	31
Total ...	65

McKee's figures[23], on the other hand, vary very considerably from those of these authors. From a series of 27 cases he records:—

Spindle-cell Sub-Type A ...	14
Epithelioid	7
Fascicular	4
Mixed	2
Total ...	27

He makes no mention of Sub-Type B. As my own figures also differ from those of Callander, and Terry and Johns, I am not going to attempt any explanation regarding the divergence in percentages recorded by McKee and the other authors quoted above.

In the present series, as already explained above, only 95 eyes were excised out of a total of 100 cases reported during the six years under review; out of these 95, three sections were missing, and the other 92 were classified in the various histological types as described by Callander[2]. It must not be assumed that the classification was easy, in most of the cases it was, but in certain cases it was found to be very difficult to decide as to which type a slide belonged. Owing to the age of the slides under examination this difficulty was further increased. To get over this difficulty, after classification by me every slide was very kindly seen by Mr. D. Shapland, the Pathologist of the Royal London Ophthalmic Hospital, and the final classification recorded is the one of which he approved. After a series of examinations, the 92 slides mentioned above were classified as:—

Spindle-cell Sub-Type A ...	22
Sub-Type B ...	7
Epithelioid	25
Fascicular	9
Mixed	29
Total ...	92

These figures differ from those of Callander, in that the incidence of Spindle sub-type A is very much higher than that of B, while he records the sub-type being the commoner of the two, also in this series epithelioid percentage is higher at the expense of the mixed-cell type, the latter fact, however, is of no consequence as both varieties are almost equally malignant.

iii.—*Quantity of pigment in various types.*

From the study of these 92 sections, the following results were arrived at:—

	None	Slight	Moderate	Heavy	Total
Spindle A	5	5	11	1	22
Spindle B	3	2	1	1	7
Fascicular	1	1	5	2	9
Epithelioid	1	1	10	13	25
Mixed	4	1	14	10	29
Total	14	10	41	27	92

Apart from the fact that spindle-cell growths show less pigment, and epithelioid and mixed-cell varieties have a tendency to contain larger quantity of pigment, I do not think any further comments are required.

VII.—Histological types and prognosis

Callander in his original paper[2] on the histological classification of sarcoma of the uvea states that in order of malignancy various types rank as follows:—

1. Epithelioid type—most malignant.
2. Fascicular—next.
3. Spindle type B—more malignant than Type A.
4. Spindle type A—least malignant.
5. Mixed type—malignancy varies with the type of cell preponderating, it is the presence of epithelioid cells which is responsible for the metastases, this type claims the largest percentage of deaths from metastases.

The same author when giving the record of 237 cases in a later paper[3] gives the following figures:—

Type of Growth	No. Cases	No. Followed	Deaths Metastases	% Dead of Metastases
Spindle A	31	25	—	0·00
Spindle B	54	44	3	6·81
Epithelioid	17	14	3	21·42
Fascicular	12	12	3	25·00
Mixed	123	101	37	36·64
Total	237	196	46	23·47

From the point of view of malignancy this author[4] divides the uveal sarcomas in two groups:—

1. More malignant group consisting of epithelioid, fascicular, and mixed cell types.

2. Comparatively benign group, spindle-cell type A & B.

Terry and Johns[34] discussing the same question from a study of 94 cases disagree with Callander as regards spindle-cell B, they state that spindle-cell sub-type B is just as malignant as epithelioid and fascicular types, they grade these tumours in three groups:—

Grade 1.—Comparatively benign spindle A.

Grade 2.—Next in order of malignancy, spindle B, epithelioid, and fascicular.

Grade 3.—Most malignant mixed-cell type.

They give the following percentages from 65 cases which they have followed for more than five years:—

Type of Growth	No. Cases	No. Deaths Metastases	% Dead of Metastases
Spindle A	6	—	0·00
Spindle B	12	5	41·5
Fascicular	8	5	41·5*
Epithelioid	8	3	37·5
Mixed	31	16	51·6
Total	65	29	41·5*

*These figures are not correct, but are copied from his tables.

In the 92 cases of this series the deaths from metastases and the percentage from the total cases are as under:—

Type of Growth	No. Cases	No. Followed	Deaths Metastases	% Dead of Metastases
Spindle A	22	22	—	0·00
Spindle B	7	4	—	As three cases are untraced, therefore no percentage can be given.
Fascicular	9	7	4	44·5
Epithelioid	25	22	9	36·00
Mixed	29	27	13	45·00
Total	92	82	26	28·26

To compare the percentage deaths from the present series with those of Callander, and Terry and Johns.—

	Present Series	Terry and Johns	Callander
Spindle A ...	0·00	0·00	0·00
Spindle B ...	None given	41·5	6·81
Fascicular ...	44·5	41·5	25·00
Epithelioid ...	36·00	37·4	21·42
Mixed ...	45·00	51·6	36·64
Total ...	28·26	41·5	23·47

The percentages of Terry and Johns, of course, are only taken from the cases which they had followed for more than five years, my figures are from the cases that were operated upon three to nine years ago.

Table showing details of 95 cases according to histological types

Cell type	Total No. Cases	Cases living				Cases dead					Cases untraced
		Over 5 years	3 to 5 years	Total living	% living	Metastases	Cause unknown	Other causes	Total dead	% Deaths due to Metastases only	
Spindle A ...	22	15	7	22	100	—	—	—	—	—	—
Spindle B ...	7	2	2	4	57	—	—	—	—	*	3
Fascicular ...	9	2	1	3	33	4	—	—	4	44·5	2
Epithelioid ...	25	4	5	9	36	9	1	3	13	36·0	3
Mixed ...	29	5	6	11	38	13	2	1	16	45·0	2
Sections lost	3	1	1	2	—	1	—	—	1	—	—
Total ...	95	29	22	51	53	27	3	4	34	28·5	10

*This percentage cannot be given as explained in the preceding Table.

From the preceding table it can be reasonably deduced that:—

1. Spindle A growths have a very good prognosis, in my series, and from the series of the authors quoted above, no death from secondary growths has been recorded in this group.

2. Fascicular, epithelioid, and mixed-cell growths each show approximately a mortality of 40 per cent. from secondary growths, the mixed-cell growths being rather worse than the other two.

3. I am unable to give an opinion regarding the spindle B growths, owing to the relatively large number of cases untraced. But assuming that some of these have died of metastases, as they probably have, then spindle B growths can reasonably be classed mid-way between the other two groups from the point of view of malignancy.

With these deductions I agree with Terry and Johns in grading these growths in three groups, but I do not agree with these authors in placing spindle B growths in parity with fascicular, and epithelioid groups from the point of view of malignancy. I also disagree with Callander when he states that this type of growth is only slightly more malignant than spindle A group. From the results of the follow-up I would suggest the following grades:—

Grade I.—Spindle sub-type A, with few or no metastases. The most benign group.

Grade II.—Spindle sub-type B, mid-way between the other two groups, definitely more malignant than sub-type A, but not so malignant as the grade III group, this is obvious from the number of survivors traced. I am unable to record the exact percentage of metastases owing to reasons given before.

Grade III.—Fascicular, epithelioid, and mixed-cell growths, with a mortality from secondary growths of about 40 per cent. The mixed-cell growths are slightly more malignant than the other two.

The total mortality from secondary growths in this series is in the neighbourhood of 30 per cent.

VIII.—Prognosis from combined study of reticulin content and histological types

Obviously the next question which arises is, can an accurate prognosis be given in spindle B, fascicular, epithelioid, and mixed-cell tumours from the reticulin content of these growths? It is presumed from the description given in the previous chapter that spindle A growths have a uniformly good prognosis. To answer this question a detailed study of all cases which have died from metastases, and of all the cases which are alive, is required.

Cases known to have died of metastases.—These tables are only prepared from those cases in which both reticulin sections and H. and E. sections were available.

RETICULIN CONTENT

Type cell	++++	+++-	++--	+---	----	Total
Spindle A ...	–	–	–	–	–	–
Spindle B ...	–	–	–	–	–	–
Fascicular ...	–	–	–	2	1	3
Epithelioid ...	–	1	1	5	2	9
Mixed ...	–	2	2	7	–	11
Total ...	–	3	3	14	3	23

From the above table it will be noticed that 20 out of 23 cases show a reticulin content of half or less than half, and 17 out of these 23 were definitely less than half.

Cases which are alive.—To compare the above with the cases which are alive, necessarily requires two sets of figures, that is the cases alive for more than five years, and the cases alive from three to five years.

These tables are only taken from those cases in which both reticulin and H. and E. results were available.

RETICULIN CONTENT

		Alive more than 5 years					Alive 3 to 5 years				
Type growth	Total	++++	+++-	++--	+---	----	++++	+++-	++--	+---	----
Spindle A ...	18	6	4	–	1	–	3	2	1	1	–
Spindle B ...	4	2	–	–	–	–	1	–	–	–	1
Fascicular...	3	1	1	–	–	–	1	–	–	–	–
Epithelioid	5	1	–	2	–	–	1	–	1	–	–
Mixed ...	8	2	1	1	–	–	–	2	2	–	–
Total ...	38	12	6	3	1	–	6	4	4	1	1

Total of the above separate figures is as follows:

RETICULIN CONTENT

Type growth	++++	+++-	++--	+---	----	Total
Spindle A ...	9	6	1	2	–	18
Spindle B ...	3	–	–	–	1	4
Fascicular ...	2	1	–	–	–	3
Epithelioid ...	2		3	–	–	5
Mixed ...	2	3	3	–	–	8
Total ...	18	10	7	2	1	38

Some interesting facts emerge from the study of these tables; these are that there is only one patient alive with total absence of reticulin, and as I have recorded elsewhere that patient was operated

upon as recently as 1935, so one may be permitted to be dubious about his future. There are only two patients alive with reticulin content of less than half (+ — — —), both of these belong to spindle sub-type A, which I have shown above as a rule gives 100 per cent. good prognosis. All the other patients who are alive contain either half (+ + — —), or more than half (+ + + —), (+ + + +). From the comparison of the tables of cases which are alive and dead, it seems reasonable to deduce that reticulin examination considerably aids the histological classification in arriving at a prognosis.

To Summarise :—

1. Spindle-cell sub-type A growths have always a very good prognosis.

2. Spindle-cell sub-type B growths when aided with reticulin content of half, or more than half give a good prognosis.

3. Fascicular, epithelioid, and mixed growths, good prognosis can only be given when the reticulin content is definitely more than half, that is that the slide must belong to group (+ + + +), or (+ + + —), the more the reticulin the better the prognosis. If the reticulin content is about half (that is + + — —), the prognosis becomes doubtful, as some cases survive, and the others succumb to metastases. And when the reticulin content falls below half (that is + — — —), or is totally absent (— — — —), a definitely bad prognosis can be foretold.

To summarise, on the next page in a table I am giving the results of follow-up of all 95 cases with details of histological classification and reticulin content examination. The information that the table yields has been discussed above. It differs from the above tables in that whereas they contained only the results of cases in which both classifications were available, this table contains the results of all the cases in which an attempt was made to trace.

To complete the table the deaths recorded should be further divided into the deaths due to secondary growth, unknown causes, and those due to other causes. Their details are as under:—

Deaths due to other causes ... ... 4 cases

Type growth	Reticulin content	Remarks
1. Epithelioid ...	— — — — ...	All these cases
2. Epithelioid ...	— — — — ...	belong to malignant
3. Epithelioid ...	Missing ...	cell-types with low
4. Mixed	+ — — — ...	reticulin content.

Deaths due to unknown cause ... ... 3 cases

1. Mixed ... ... Missing
2. Epithelioid ... ... + + + +
3. Mixed ... ... Missing

Reticulin Groups	Spindle A				Spindle B				Fascicular				Epithelioid				Mixed				Total*			
	Living	Dead	Untraced	Total	Living	Dead	Untraced	Total	Living	Dead	Untraced	Total	Living	Dead	Untraced	Total	Living	Dead	Untraced	Total	Living	Dead	Untraced	Total
Group I (+ + + +)...	9	—	—	9	3	—	—	3	2	—	1	3	2	1	—	3	2	—	—	2	18	1	1	20
Group II																								
A (+ + + -) ...	6	—	—	6	—	—	2	2	1	—	—	1	—	1	—	1	3	2	—	5	11*	3	2	16*
B (+ + - -) ...	1	—	—	1	—	—	—	—	—	—	—	—	3	1	—	4	3	2	—	5	7	3	—	10
C (+ - - -) ...	2	—	—	2	—	—	1	1	—	2	1	3	—	5	—	5	—	8	—	8	2	15	2	19
Group III (- - - -)	—	—	—	—	1	—	—	1	—	1	—	1	—	4	1	5	—	—	—	—	1	5	1	7
Total	18	—	—	18	4	—	3	7	3	3	2	8	5	12	1	18	8	12	—	20	39	27	6	72
Eyes missing ...	4	—	—	4	—	—	—	—	—	1	—	1	4	1	2	7	3	4	2	9	12*	7*	4	23
Grand Total ...	22	—	—	22	4	—	3	7	3	4	2	8	9	13	3	25	11	16	2	29	51	34†	10	95

Total No. Investigated ... 95

*Includes 3 cases not grouped under cell classification, 1 in Group II A living, 1 in eyes missing dead, and 1 in eyes missing living.
†Causes of deaths—metastases 27, unknown causes 3, other causes 4. Details on page 271.

IX.—Sarcoma of the uvea—Is there a time limit after which a cure can be assumed

The prognosis of sarcoma of the uvea is always very uncertain. The greatest difficulty in arriving at some conclusion is the fact that there seems to be no time limit after which secondary growths may not occur. E. von Hippel's[17] observation, "There is no limit after which a cure can be assumed," has been proved time and again by him and other workers on the subject. The same author[17], however, in recording 23 cases which he has followed for more than ten years, states that 22 are either alive or have died from some other disease, and only one has succumbed to metastases. In the same paper while describing a series of 189 cases, he records that 17 per cent. of the survivors died after five years, and 10 per cent. after ten years. He follows up the same subject in subsequent papers[18] where he shows that 65 of his cases lived for more than five years, 45 for more than ten years, and 11 for more than twenty years, in the translation, however, which I possess, it is not mentioned how many of these died of secondary growths, and how many from other causes.

Considering the small number of metastases after ten years he comes to the conclusion[19] that "A ten year limit must therefore be taken as a basis if a clinical cure is to be mentioned at all." In support of this contention he records that in his series, 37 deaths from metastases occurred within five years of enucleation, 13 from five to nine years after, and only three after ten years[19].

Teraskeli[33], on the other hand, considers four years long enough to assume permanent cure. In his series 68 (4 per cent.) were alive after four years, 21 (1 per cent.) and 10 per cent. had had metastases and recurrences respectively. Incidently in the same paper he goes on to say that "histological differences seem to have no particular effect on prognosis," which statement is quite contrary to what I have recorded in the previous chapters.

Choun[5] discussing his 61 cases, records 14 deaths, three of them lived for more than five years.

Denecke[10] in his report on 36 cases, records 14 deaths, 11 within five years, two in 6th and 7th year, and one 14½ years after enucleation.

Terry and Johns[34] also came to the conclusion that a five year rule is of no use, as they have also recorded six deaths in their series of 94 cases after this period, four out of these occurred 9 to 12 years after enucleation.

From the figures quoted above it is clear that a certain number of metastases do occur after five years, but that number is relatively small, and therefore a patient who has passed the five year limit can to a certain extent be assumed to be safe from secondary

growths, although an absolute assurance to this effect cannot be given after ten years.

In the present series, as I have recorded elsewhere, 27 cases died of metastases, the time interval between the operation and death is as under :—

Within 1 year	...	4 cases
1–1½ years ...	...	7 cases
1½–2 years ...	...	3 cases
2–2½ years ...	...	2 cases
2½–3 years ...	...	3 cases
3–4 years ...	...	3 cases
4–5 years ...	...	1 case
Over 5 years ...	...	Nil.
Interval unknown	...	4 cases
Total ...	27 cases	

The earliest death in this series was six months after the operation.

It will be noticed from the above table that 11 out of 23 cases whose date of death is known died within 18 months of enucleation, one after four years, and none after five years, so perhaps it is reasonable to assume that very few deaths occur after a patient has passed the five year limit, so I am inclined to agree with Teraskeli[33] in regarding the four year period as a basis for permanent cures.

In this series I am not able to give the time interval after which the metastases were first noticed, but it appears from the dates of deaths of various cases that the statement of Schovanic[30], "The majority of metastases occur in the first three months after enucleation," does not allow a long enough time, E. von Hippel is nearer the mark when he states[18] "most metastases occur in the first year after enucleation," and that very late metastases can be considered as relative cures.

I have recorded in the previous chapters that 51 cases out of the 95 cases operated upon at Moorfields were alive at the time of this enquiry, the periods for which they have been living obviously free from the disease are as follows :—

Year	No. cases	No. living	Alive for
1930 ...	11 ...	5 ...	8 years
1931 ...	18 ...	7 ...	7 years
1932 ...	20 ...	11 ...	6 years
1933 ...	13 ...	6 ...	5 years
1934 ...	13 ...	11 ...	4 years
1935 ...	20 ...	11 ...	3 years
Total ...	95	51	3 to 8 years

In the above table, in the total number of cases, no account has been taken of the cases that have not been treated, or of one private case which was not traced, and in the cases living only those are included

which were known to be alive. One patient although living was known to be suffering from metastases and is counted under deaths. The percentage worked below is calculated accordingly.

So it will be noticed that 29 cases out of 62 (total for the years 1930 to 1933) were alive for more than five years, that is 48·4 per cent., not taking into consideration the cases which have not been traced or have died from other disease. E. von Hippel[19] taking all these factors in consideration, and after following up his series for a number of years, some of them for over 20, has come to the conclusion that approximately 45 per cent. of all sarcoma cases die of secondary growths.

X.—Early diagnosis and prognosis in sarcoma of the uvea

Most of the writers while discussing the prognosis in uveal sarcoma are agreed on the statement that the "earlier the operation the better the prognosis," (Teraskeli[33], Renard[27], Choun[5], Schovanic[30], Sir J. Parsons[26], and other authors of text-books on ophthalmology). But a discordant note has been sounded by E. von Hippel[17] who writes that "It is not yet possible to state that early enucleation gives a good prognosis, and late enucleation a bad one." He, while analysing his cases, shows that whereas among 609 cases with 162 metastases, the metastases are approximately equally distributed between the three stages at which the enucleation was performed, E. von Hippel in his own 84 cases finds that out of the 33 which had metastases, 14 occurred in 41 cases of I stage (34 per cent.), 16 in 34 cases of II stage (47 per cent.), and 3 among 8 cases of III stage (37 per cent.) thus II stage with 47 per cent. comes out worst as far as the incidence of metastases is concerned. He also adds that among his own 58 cases observed for 5 to 23 years the great majority of those treated during the first stage are well, but on taking into consideration all the 189 cases, most of the survivors are found in the second stage, but also the largest (absolute) number of metastases are found in the same stage. E. von Hippel, with many other workers, has recorded very early metastases in cases in which diagnosis and treatment was carried out very early in the disease, and the converse also holds good.

Jaensch[21] does not agree with von Hippel that metastases are more frequent after enucleation in II stage than after enucleation in I stage, and also he confirms the fact that extension of the tumour to the sclera does not necessarily pave the way to metastases. In his series, 21 cases were operated upon in the 1st stage, 11 out of these have passed the 5th year, and 4 have passed the 10th year. Eight cases were operated upon during the 2nd stage, 4 out of these have passed the 5th year, and 2 the 10th year.

Schovanic[30] in his paper fully reports two cases of sarcoma of the ciliary body, one of which resulted in death in spite of very early diagnosis and enucleation, and the other showed no sign of metastases six years after operation although the tumour had already existed for two years before the operation was performed.

Teraskeli[33] reports two cases of sarcoma of the choroid, and neither of these was treated, and yet they did not die of metastases (after 7 years and $2\frac{1}{2}$ years respectively).

There can hardly be a dissention to the fact that the moment sarcoma is diagnosed, it must be operated upon, whether the operation is enucleation, evisceration or exenteration of the orbit, followed or not followed by irradiation depending upon the stage of the disease and the choice of the operator, but on the other hand it must be understood that a late diagnosis (resulting in a late operation) does not necessarily mean a bad prognosis as is evidenced by the writings of the authors quoted above, and the following examples in this series:—

1. Female, aged 76 years, eyeball excised in May 1931, at operation a very large extra-ocular extension of the growth was found, the orbit was exenterated, and later treated by radium. This patient is still alive with no sign of metastases or recurrence, she is now 84 years of age, and operation was performed seven years ago.

Histological classification.—Mixed-cell growth with spindle sub-type B very largely preponderating.

Reticulin content:— + + + — (Group 2 A).

There are four other cases in this series of gross extra-ocular extension, and they have all died of metastases, they all belonged to either epithelioid or mixed-cell groups with low reticulin content.

2. There were 22 patients with microscopic evidence of extra-ocular extension either along veins or ciliary nerves, and in one case along the optic nerve, 14 of them are still alive, and 7 of the 14 have passed the fifth year.

3. Scleral involvement by itself does not seem to influence the prognosis either way. There were several cases in this series in which scleral infiltration was present in varying degree, I am unable to draw the deduction that the prognosis in these cases is any worse than the cases in which the sclera was not involved.

It is perhaps as well to emphasise here the importance of scleral barrier against extension of the sarcoma. (Cozza F.[8])

There is one subject which still requires mention, that is one often finds early or late metastases in the cases which have been diagnosed and treated in a very early stage, in cases in which the growth is small and limited, and there is no microscopic evidence

of extension along any known channel, and in cases in which there is no scleral infiltration, it is obvious that transplantation of tumour cells in these cases must have occurred before the eyeball was excised, if that is the case then why such late metastases? Obviously in these cases the tumour breaks through the blood vessels at an early stage, the enucleation is done too late to prevent it, and these transported cells remain latent in other organs for a long time. E. von Hippel [17 18] and Jaensch[21] emphasise the importance of body resistance in these cases, and it appears that evidently the body can "deal with" a few transported cells (von Hippel). This fact might explain the occurrence of very late metastases, in some cases 10 or 15 years after the original disease, the explanation lies in the ability of the body to prevent the growth of these transported cells for a very long time.

XI.—Conclusions

From the preceding pages and the facts and figures quoted therein it seems reasonable to infer that Callander.[2 3] and Callander and Wilder[4] have made a very important contribution towards the solution of this very vague problem, the prognosis in sarcoma of the uvea. It also seems reasonable to conclude from the authors quoted in the previous chapter, that good results in many cases are due, not so much to early diagnosis and treatment, as to other factors, such as reticulin content of the growth and its histological type. Early diagnosis does play a part, but a subsidiary part only, as there are many cases in which the diagnosis and enucleation were carried out in the first stage of the disease, yet the patient succumbed to secondary growths. From the series published by Callander,[2 3] Terry and Johns,[34] and McKee,[23] histological cell-type classification has definitely established a place for itself in the pathology of the uveal sarcoma, I mean as regards the prognosis, the same, however, cannot yet be said of the reticulin content basis. For the latter further records and statistics over a large number of years are necessary.

To recapitulate, three grades of malignancy can be distinguished from the histological types:—

Grade I.—Spindle type A, comparatively a benign type, in so far as if other circumstances such as early diagnosis and treatment are favourable, there is hardly any death recorded from metastases in this group.

Grade II.—Spindle type B, more malignant than type A, but less malignant than other types.

Grade III.—Fascicular, epithelioid, and mixed-cell types, very much more malignant than the other types, showing a mortality of about 40 per cent., the last named is more malignant than the other two.

Reticulin content seems to influence the prognosis considerably, and it is possible by the examination of argyrophile fibres to determine the prognosis very much more accurately, as to which patient is likely to survive from, and which patient is likely to succumb to, metastases in malignant types.

From the examination of both, that is combined study of histological types and reticulin, it should be possible to foretell the prognosis in a very large number of cases, further checking and rechecking is required before a final verdict is delivered. As I have quoted several times in the text following these cases for a period of 3 to 8 years is not sufficient, as many observers have shown that metastases occur after this period.

The total mortality from secondary growths in this series works out at approximately 30 per cent., E. von Hippel records that it is 45 per cent., he has of course followed his cases over a large number of years, some of them for over 20.

XII.—Sarcoma of the iris—prognosis in

Prognosis in sarcoma of the iris is relatively better than the prognosis in sarcoma of the other parts of uvea. For instance, E. von Hippel[18] records 4 cases of sarcoma of the iris alive for 10, 21, 23, and 25 years respectively, Denecke[10] reports two cases of sarcoma of iris in his series of 36 cases, and both of them are alive for $12\frac{1}{2}$ and $4\frac{1}{2}$ years respectively.

In this series there are four cases of sarcoma of the iris, and none of them is known to have died of metastases; in the case of one patient the eye was not excised at Moorfields. The results of follow-up in these cases are:—

Alive (for 8 years) ...	1
Dead from other causes ...	1
Lost (untraced)	1
Eyes not excised	1
Total	4

In the three excised eyes the type of cell found in all of them was epithelioid, and only in one case reticulin content could be calculated, as the other two blocks were missing.

The reticulin content, histological cell-types, the year of operation, and the results of follow-up are as under:—

Year Operation	No. Case	Histological Type	Reticulin Content	Result Follow-up
1930 ...	1 ...	Epithelioid ...	++++ ...	Alive
1933 ...	2 ...	Epithelioid ...	Missing ...	Dead (other cause)
1933 ...	3 ...	Epithelioid ...	Missing ...	Lost
1933 ...	4 ...	Eye not excised, and not traced		

It is obvious from the above that in view of the fact that I found only one patient alive, one dead from other causes, and one untraced patient, I am not in a position to give any views about prognosis in sarcoma of the iris.

APPENDIX I—*Statistics.*

As already explained in the previous chapters 100 patients suffering from sarcoma of the uvea were admitted to the Royal London Ophthalmic Hospital during the years 1930 to 1935 both inclusive.

TABLE I—*Showing the number of cases by years.*

1930	... ...	11
1931	... ...	18
1932	... ...	20
1933	... ...	16
1934	... ...	14
1935	... ...	21
Total	...	100

1. TABLE II—*Showing the percentage incidence of sarcoma to the New Out-patients during the period, that is the percentage incidence to all eye diseases.*

Year	Sarcoma cases	New Out-patients	Percentage of Sarcoma to all eye diseases	or one case of Sarcoma in every
1930	11	46,517	0·024	4,229
1931	18	44,282	0·0407	2,460
1932	20	47,078	0·0425	2,354
1933	16	47,915	0·0334	2,995
1934	14	51,672	0·027	3,691
1935	21	53,712	0·039	2,558
Total	100	291,176	0·0343	2,913

TABLE III—*Showing percentage incidence of sarcoma to all Out-patients, new and old, the latter with first attendance in the year. (Percentage to all eye diseases).*

Year	Sarcoma Cases	New Out-Patients	Old Out-Patients	Total Out-Patients	Percentage of Sarcoma to all eye diseases	or one case of Sarcoma in every
1930	11	46,517	5,855	52,372	0·021	4,761
1931	18	44,282	5,792	50,074	0·036	2,782
1932	20	47,078	6,658	53,736	0·037	2,687
1933	16	47,915	7,177	55,092	0·029	3,443
1934	14	51,672	6,831	58,503	0·024	4,179
1935	21	53,712	8,288	62,000	0·034	2,952
Total	100	291,176	40,601	331,777	0·03	3,318

In this series the incidence works out as 1 in 3,000, it is higher than the ones previously recorded at Moorfields, but lower than the ones recorded by several other observers. The percentage in this series works out as 0·03 per cent. of all eye diseases. The other figures are:—

Stallard[32] gives it as 1 in 4,000 at Moorfields; Fuchs[16A] 0·066 of all eye diseases; Davenport[9] in his series of 35 cases says that the incidence at Moorfields is 2 in 10,000, but he says the usual incidence is 3 to 6 per 10,000; Terry and Johns,[34] 5 in 10,000.

2. TABLE IV—*Showing percentage In-patients for sarcoma to total In-patients at Moorfields.*

Year	Sarcoma In-Patients	Total In-Patients	% Sarcoma In-Patients to total In-Patients	or one Sarcoma Patient to every
1930	11	2,547	0·432	232
1931	18	3,133	0·575	174
1932	20	3,276	0·61	164
1933	16	3,279	0·488	205
1934	14	3,263	0·429	233
1935	21	3,739	0·56	178
Total	100	19,237	0·52	192

So approximately for every 200 in-patients in the hospital (Moorfields) there is one admission for sarcoma of the uvea, to be exact a percentage of 0·52.

3. AGE INCIDENCE—TABLE V—*Showing the incidence of sarcoma in different age-groups.*

Year	Sarcoma Cases	Age 20—30	Age 31—40	Age 41—50	Age 51—60	Age 61—70	Age over 70	Age not known
1930	11	1	–	2	3	1	2	2
1931	18	3	3	2	4	1	3	2
1932	20	2	2	6	4	5	1	–
1933	16	–	3	1	5	4	2	1
1934	14	–	1	4	3	5	1	–
1935	21	–	2	6	5	6	2	–
Total	100	6	11	21	24	22	11	5

The youngest patient in the series was 26 years of age; the oldest patient in the series was 77 years of age.

From the above table it will be noticed that the optimum as regards the incidence of sarcoma is concerned is in the decade 50-60 years with a total of 24 cases in this series, the decade before it (*i.e.*, 41-50) accounts for 21 cases, and the decade after it (61-70) for 22 cases, the years 41-70 show 67 cases out of 100, that is 67 per cent., while in the years preceding these and following these there is a sharp fall in the incidence.

TABLE VI—*Showing average age in this series.*

Year	Average age
1930	55·33
1931	50·19
1932	50·95
1933	56·27
1934	56·21
1935	54·76
Average for the whole series ...	53·70

Average age as given by other authors:—

Lawford & Collins	48·42
Marshall	54·63
Davenport	50·4
Fuchs	44·2

4. SEX INCIDENCE—TABLE VII—*Showing the incidence in both sexes.*

Year	Sarcoma cases	Males	Females	Not known
1930 ...	11 ...	6 ...	5 ...	–
1931 ...	18 ...	10 ...	8 ...	–
1932 ...	20 ...	7 ...	13 ...	–
1933 ...	16 ...	7 ...	8 ...	1
1934 ...	14 ...	6 ...	8 ...	–
1935 ...	21 ...	8 ...	13 ...	–
Total ...	100	·44	55	1

Davenport in his series of 35 cases records 12 males and 23 females, that is 34·3 per cent. and 65·7 per cent. respectively, but he adds that in 345 cases at Moorfields up to that date there were 167 males and 175 females, sex not known in three cases.

In the present series males and females are affected in the proportion of 44·4 per cent. and 55·6 respectively.

5. VARIOUS PARTS OF UVEA AFFECTED—TABLE VIII—*Showing the incidence in various parts of uvea.*

Year	Sarcoma Cases	Choroid	Choroid and Ciliary Body	Iris
1930 ...	11 ...	8 ...	2 ...	1
1931 ...	18 ...	16 ...	2 ...	–
1932 ...	20 ...	17 ...	3 ...	–
1933 ...	16 ...	13 ...	– ...	3
1934 ...	14 ...	11 ...	3 ...	–
1935 ...	21 ...	18 ...	3 ...	–
Total ...	100	83	13	4

So in this series the choroid, ciliary body, and iris are affected in the following percentages respectively, 83 per cent., 13 per cent., and 4 per cent. These figures more or less agree with those of Fuchs who records choroid affected in 85 per cent., ciliary body in 9 per cent., and iris in 6 per cent. of his 259 cases.*

The figures given by other workers are:—

Iris.	Martin*	...	1 in 43 cases.
	Collins*	...	1 in 103 cases.
	Fuchs*	...	16 in 259 cases (6 per cent.)
	Teraskeli[33]	...	No cases in 33.
Ciliary Body.	Fuchs*	...	22 in 259 cases (9 per cent.)
	Teraskeli[33]	...	2 in 33 cases.

6. SUMMARY.

1. Incidence of sarcoma to all eye diseases, 0·3 per cent., or 1 in 3,000 cases.

2. Incidence of sarcoma in-patients to all in-patients, 0.52 per cent., or 1 in 200 cases.

3. Average age for sarcoma of the uvea, 53·70.

4. Incidence in sexes, males 44·4 per cent., females 55·6 per cent.

5. Various parts of uvea affected—choroid, 83 per cent.; iris, 4 per cent.; ciliary body, 13 per cent.

APPENDIX II—*A list of all cases living with their histological types and reticulin content.*

SUMMARY.

Alive	51	Deaths, metastases ...	27
Patients untraced ...	10	Dead, other causes ...	4
Eyes not excised... ...	4	Dead, unknown cause ...	3
Not attempted to trace ...	1		
Total ...	100		

List of patients alive on September 1, 1938.

Year Op.	Serial No.	Ref. No.	Histological type	Reticulin content
1930 ...	1 ...	1 ...	Spindle type A ...	+ + + −
	2 ...	7 ...	Spindle type A ...	+ + + +
	3 ...	12 ...	Mixed spindle A ...	+ + − −
	4 ...	92 ...	Epithelioid	+ + + +
	5 ...	96 ...	Mixed spindle B ...	+ + + +

* Pathology of the Eye by Sir J. Parsons. Edition 1904.

Year Op.	Serial No.	Ref. No.	Histological type	Reticulin content
1931	6	14	Spindle type A	+ + + +
	7	15	Mixed spindle B	+ + + +
	8	18	Spindle type A	+ + + +
	9	20	Spindle type A	+ − − −
	10	21	Mixed spindle B	+ + + −
	11	22	Fascicular	+ + + −
	12	23	Spindle type A	+ + + −
1932	13	29	Spindle type B	+ + + +
	14	33	Missing	+ + + −
	15	36	Spindle type A	Missing
	16	38	Spindle type A	+ + + −
	17	39	Spindle type A	+ + + −
	18	40	Spindle type A	+ + + +
	19	41	Spindle type A	+ + + +
	20	42	Epithelioid	+ + − −
	21	44	Mixed All	Missing
	22	45	Spindle type A	+ + + +
	23	46	Spindle type B	+ + + +
1933	24	50	Epithelioid	Missing
	25	51	Spindle type A	Missing
	26	53	Spindle type A	Missing
	27	56	Spindle type A	Missing
	28	58	Epithelioid	+ + − −
	29	59	Fascicular	+ + + +
1934	30	60	Spindle type A	+ + + −
	31	61	Epithelioid	Missing
	32	63	Missing	Missing
	33	64	Spindle type A	+ + + −
	34	66	Spindle type B	+ + + +
	35	67	Mixed Epithelioid	Missing
	36	68	Mixed Spindle B	+ + + −
	37	69	Epithelioid	Missing
	38	70	Spindle type A	+ − − −
	39	71	Mixed All	Missing
	40	98	Epithelioid	Missing
1935	41	72	Fascicular	+ + + +
	42	73	Mixed Epithelioid	+ + − −
	43	75	Spindle type A	+ + − −
	44	78	Mixed Spindle A	+ + − −
	45	80	Epithelioid	+ + + +
	46	81	Epithelioid	+ + - -
	47	82	Spindle type A	+ + + +
	48	83	Mixed All	+ + + −
	49	87	Spindle type B	- - - -
	50	90	Spindle type A	+ + + +
	51	91	Spindle type A	+ + + +

Case No. 12 had a very large extra-ocular extension.

Note.—After the mixed-cell growths, the cell which is found in largest numbers (the preponderating cell) is mentioned. In the slides in which all varieties were almost equally distributed the expression 'mixed all' is used.

APPENDIX III—*A list of all cases dead with their histological types and reticulin content.*

SUMMARY.

Dead Metastases	...	27
Dead, other causes	...	4
Dead, unknown cause	...	3
Total Dead	... ...	34

List of cases which died of metastases.

Year Op.	Serial No.	Ref. No.	Histological type	Reticulin content	Date death
1930	1	4	Mixed spindle A	+ — — —	7/1933
	2	6	Mixed spindle B	+ + — —	7/1931
1931	3	8	Epithelioid ...	+ + — —	3/1935
	4	9	Epithelioid ...	+ — — —	—
	5	17	Epithelioid ...	— — — —	6/1934
	6	25	Mixed Epithelioid ...	+ + + —	—
	7	27	Mixed all ...	+ — — —	—
	8	19	Mixed Spindle B	+ — — —	4/1933
1932	9	28	Epithelioid ...	+ — — —	12/1933
	10	30	Epithelioid ...	+ + + —	1/1935
	11	31	Mixed all ...	+ + — —	6/1936
	12	34	Epithelioid ...	— — — —	6/1933
	13	43	Mixed spindle B	+ + + —	after 2 yrs.
	14	47	Epithelioid ...	+ — — —	after 1¼ yrs.
1933	15	48	Mixed epitheloid	Missing	6/1937
	16	54	Mixed spindle B	+ — — —	7/1935
	17	57	Fascicular ...	+ — — —	11/1935
1934	18	62	Missing ...	Missing	9/1935
1935	19	74	Mixed epithelioid	+ — — —	9/1936
	20	76	Mixed spindle B	+ — — —	6/1938
	21	77	Fascicular ...	+ — — —	2/1937
	22	79	Fascicular ...	— — — —	—
	23	84	Fascicular ...	Missing	4/1938
	*24	85	Epithelioid ...	+ — — —	Alive
	25	86	Epithelioid ...	+ — — —	2/1936
	26	88	Mixed all ...	Missing	2/1936
	27	89	Mixed all ...	+ — — —	Winter 1935

* This patient though still alive is definitely suffering from secondary growths, and hence she is classed under deaths from metastases.

List of cases dead from other causes.

Year Op.	Serial No.	Ref. No.	Histological type	Reticulin content	Date death
1930	1	5	Epithelioid ...	— — — —	9/1934
1932	2	32	Epithelioid ...	— — — —	after 5 yrs.
1933	3	93	Epithelioid ...	Missing	6/1935
1934	4	65	Mixed spindle B	+ — — —	10/1937

List of cases dead from unknown causes.

1931 ...	1 ...	13 ...	Epithelioid ...	... + + + + ...	—
1932 ...	2 ...	37 ...	Mixed spindle B	... Missing	...	—
1933 ...	3 ...	52 ...	Mixed all ...	... Missing	...	10/1936

Note.—See note on the foot of page 283.

APPENDIX IV—*List of cases which could not be traced with their histological types and reticulin content.*

Year Op.	Serial No.	Ref. No.	Histological type	Reticulin content
1930 ...	1 ...	2 ...	Fascicular	+ + + +
	2 ...	3 ...	Fascicular	+ — — —
1931 ...	3 ...	10 ...	Spindle type B ...	+ + + —
	4 ...	11 ...	Spindle type B ...	+ — — —
	5 ...	16 ...	Epithelioid	Missing
	6 ...	24 ...	Mixed spindle B ...	Missing
	7 ...	26 ...	Mixed spindle A ...	Missing
1932 ...	8 ...	35 ...	Spindle type B ...	+ + + —
1933 ...	9 ...	55 ...	Epithelioid	— — — —
	10 ...	94 ...	Epithelioid	Missing

See note on the foot of p. 283.

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VITAMIN "C" (ASCORBIC ACID)—ITS THERAPEUTIC VALUE IN INFLAMMATORY CONDITIONS OF THE CORNEA

BY

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and

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ALTHOUGH during the past six years a certain amount of research work has been carried out upon the somewhat doubtful relationship of vitamin "C" to the development of cataract, little attention has been given to the therapeutic value of this vitamin in certain other ocular diseases, namely, inflammation and ulceration of the cornea.

It has been held that the administration of vitamin "C" to patients suffering from certain types of cataract has met with some slight improvement in the visual acuity.[1] Further, it has been

shown that the cataractous lens contains a decreased amount of ascorbic acid,[2] and that in a case of cataract the level of ascorbic acid is usually low in the urine, although it is normal in the blood.

It has been suggested, however, that the low ascorbic acid content of the lens might be the result of the cataractous changes rather than the underlying cause, and that the improvement of the vision noted in certain instances on treatment with ascorbic acid might be due to its effect on the media of the eye, the retinal vessels and the optic nerve.[3]

Experimental work on the effects of liquid mustard gas on the eyes of rabbits by Livingston and Walker[4] showed that ascorbic acid given intravenously was of value in the treatment of the corneal lesions. The results of further work on this subject by Ida Mann and Pullinger[5] showed, however, that from their experiments the value of ascorbic acid in counteracting the effects of gas keratitis was not apparent.

It was at the suggestion of Group Captain Livingston that the authors of this paper, working independently at two separate R.A.F. hospitals, have used large doses of ascorbic acid in the treatment of inflammatory conditions of the cornea.

Ascorbic acid is known to exist in high concentration in the lens and cornea of the human subject. It is a substance belonging to the group known as "redox potentials," which maintains a fine balance between the processes of reduction and oxidation, by acting either as a reducing or oxidising agent, whichever action is called for. It is therefore suggested that by introducing excess of ascorbic acid into the system the metabolism of the cornea might be accelerated, and in consequence the healing of inflammatory conditions of that structure hastened.

We have used ascorbic acid in the treatment of all cases in which severe inflammatory conditions of the cornea have necessitated in-patient hospital treatment, since the beginning of October, 1940.

The following records give details of each case.

It will be observed that in all instances the usual local treatment was given in addition to the injections of ascorbic acid, and also that in most cases local treatment alone was carried out over a period of time before using ascorbic acid.

CASE 1. Corporal F. W. T., aged 35 years—Mechanic. ***Dendritic corneal ulcer.*** On October 7, he reported sick complaining of an inflamed right eye, which he had first noticed on the previous day. He was treated with boric lotion at his sick quarters. When seen by one of us two weeks later he had a large dendritic ulcer of the cornea of the right eye. It occupied the central part of the cornea, with branches extending upwards and downwards. The vision of his right eye was 6/24. The left eye was normal, and the vision 6/5.

He was admitted to hospital at once, and the right eye was

treated with ung. atropine 1 per cent., pad and bandage. A slight improvement occurred for a few days, but a relapse subsequently took place, the ulcer becoming deeper and more extensive. Ung. scarlet red was tried, but little improvement resulted.

Thorough investigation for possible septic foci was carried out, but nothing abnormal was discovered. The Wassermann reaction of the blood was negative.

The eye became irritable to atropine, so ung. hyoscine ½ per cent. was used instead.

On November 28, the ulcer was cauterised with pure carbolic acid. Slight improvement occurred but was not maintained.

On December 20 (10½ weeks after the onset of the ulcer), ascorbic acid treatment was commenced and was given intravenously as follows :—

December 20	...	250 mgms.
,, 22	...	,, ,,
,, 23	...	,, ,,
,, 24	...	500 ,,
,, 25	...	,, ,,
,, 26	...	,, ,,
,, 27	...	,, ,,
,, 28	...	,, ,,
,, 30	...	,, ,,
,, 31	...	,, ,,

During this period the local treatment was continued. The progress made on the treatment with ascorbic acid was remarkable. The eye began to improve on the day following the first injection, and thereafter made steady progress. By December 31 (10 days after the first injection) the ulcer had completely healed, leaving only a faint superficial scar. Vision was 6/12, and the eye was almost white.

Until his discharge from hospital on January 4, he was given ascorbic acid tablets ii t.d.s. (each tablet—250 mgms.). Up to date there has been no further ulceration, and the eye has remained quiet.

CASE 2. Flying Officer J. T., aged 24 years—Czech Officer. *Disciform Keratitis.* This officer was first seen towards the end of July 1940 when the left eye was irritable. There was small corneal infiltration, and the vision was 6/18. The inflammation had commenced when he was in France three or four weeks previously, and gutt. argyrol had been prescribed. Treatment with lot. ac. boric and gutt. atropine 1 per cent. was instituted, but the condition deteriorated gradually, and he was admitted to hospital on August 15, 1940. The right eye was normal.

There was then pronounced ciliary injection with a large infiltration of the cornea containing a round dense nebula. No focal

sepsis was discovered. The B.S.R. was normal and the Meinicke reaction was negative. In spite of several forms of local treatment, the eye became steadily worse and presented a clinical picture of disciform keratitis, the vision being reduced to finger counting at one metre.

On October 22, 1940 he was given 500 mgs. of ascorbic acid intravenously, and this was repeated at intervals of 48 hours until November 1, 1940. In all he was given 3 grammes of ascorbic acid. Two days after the initial injection the eye was less irritable. By November 2, 1940 the eye was quiet and free from pain, though there was little change in the condition of the cornea. The improvement was maintained and the cornea cleared, at first slowly, then more rapidly. On discharge from hospital on December 3, 1940 the eye was white, the cornea showed only a thin paracentral nebula with a slightly denser centre 1 mm. in diameter, and the vision was 6/6. Re-examination two months later showed that the eye was still quiet.

CASE 3. Leading Aircraftsman M. K., aged 25 years.—Polish Airman. *Scleritis with early sclerosing keratitis.* Admitted to hospital October 11, 1940, The left eye had been inflamed for approximately six months, and there had been previous similar attacks over a period of three years.

There was considerable conjunctival injection with a slightly raised area of dull purplish colour over the ciliary region at two o'clock and a smaller one at seven o'clock. The deep vessels in these regions showed considerable engorgement. The cornea showed an opacity of moderate density towards the temporal side of the pupillary area, and three white superficial patches of sclerosis spreading from the limbus in the neighbourhood of the larger scleritic focus. The eye was amblyopic but showed a normal fundus. Meinicke's reaction was negative. The right eye was normal.

Local treatment was instituted with boric lotion and ung. atropine with hyd. oxid. flav. a.a. 1 per cent. sodium salicylate was given by the mouth. Two courses of short wave diathermy were given, the first being followed by temporary amelioration, but with that exception there was no improvement. Ascorbic acid was first given (500 mgs. intravenously) on November 13, 1940 and this repeated on alternate days up to November 21, 1940. During these eight days the inflammation subsided rapidly, the pain ceased and the cornea became clearer.

The improvement was maintained up to December 10, 1940 when there was a return of redness and irritability of the eye, which increased for three days. Five further injections were given between December 14 and December 21, 1940 resulting in improvement. After this treatment the eye remained quiet, and on the patient's discharge to his Unit on January 4, 1941, it was white

except for dull discolouration at the sites of scleritis. Examination with the slit-lamp revealed one faint paracentral nebula, apart from which the cornea was clear. Altogether 5 grammes of ascorbic acid were administered. He was re-examined on March 18, 1941, and it was reported that the eye was still quiet.

CASE 4. Aircraftsman R. D., aged 29 years. ***Superficial punctate keratitis.*** Admitted to hospital December 12, 1940. The right eye had been painful and inflamed for six weeks. Boric irrigations had been employed at his station sick quarters, but no improvement had resulted.

Six small superficial infiltrations were present in the lower half of the cornea, and there was moderate circum-corneal and conjunctival injection, the lower fornix being especially velvety. The patient complained of some pain, and there was profuse lacrimation. A conjunctival swab gave no growth on culture. The Wassermann reaction was negative, and no septic focus was found. Treatment with gutt. atropine 1 per cent. and spoon-bathing was instituted, and four injections of ascorbic acid (2 grammes in all) were given between December 14 and December 18, 1940. After the second injection the eye showed great improvement and the lacrimation was less. By December 19, 1940 the eye was quiet and showed only faint corneal opacities which had disappeared by December 30, 1940, though the lower fornix was still slightly oedematous.

CASE 5. Aircraftsman H. R. V., aged 26 years. ***Post vaccinial keratitis.*** Admitted to hospital January 13, 1941. Three weeks earlier he had been vaccinated, and the wound on his arm had become infected. This was followed by pain and inflammation of the left eye. He had been under treatment at his station hospital from January 4, 1941.

On admission, the left eye showed pronounced ciliary injection. There was a band-shaped infiltration 5 mm. long by 2 mm. wide in the upper part of the cornea. The iris appeared slightly discoloured, and the anterior chamber deep. Pain and lacrimation were prominent. On the left upper arm was a healing ulcer.

A conjunctival swab gave no growth on culture. The vitamin C content of the urine was 0·4 mg. per cent. (increased after treatment). Local treatment consisted of irrigations, atropine 1 per cent. drops and spoon-bathing. No appreciable improvement resulted. Injections of ascorbic acid were started on January 20, 1941. On January 24, 1941 the eye was considerably quieter, and this improvement was maintained. By February 10, 1941 the eye was quiet with neither pain nor lacrimation. On discharge on February 17, 1941 the eye was white and there was no trace of corneal scarring. The arm ulcer had healed. He was given 2·5 grammes ascorbic acid in five injections.

CASE 6. Aircraftsman D. S. W., aged 26 years. ***Phlyctenular***

keratitis. Admitted January 27, 1941. His left eye had been inflamed for three months, treatment having been carried out at his station sick quarters with irrigations and atropine.

The pupil was semi-dilated and slightly active; there was moderate conjunctival and ciliary injection; and the cornea showed several diffuse superficial infiltrations, phlyctenular in type, but without vascularisation. The vitamin C content of the urine was 0·7 mg. per cent. which did not increase. A conjunctival swab provided a few colonies of staphylococcus albus. The local treatment was continued, and 2 grammes of ascorbic acid administered in four injections.

The eye settled down rapidly. The infiltrations faded, and when the patient was discharged on February 19, 1941, they were barely perceptible.

CASE 7. Aircraftsman T. F. B., aged 22 years. ***Superficial punctate keratitis.*** On February 3, 1941, the left eye was injured by a twig. It became red and painful two days later. He was admitted to hospital on March 14, 1941. The left eye showed much conjunctival and ciliary injection with a group of small subepithelial infiltrations of the cornea. There was blepharospasm and copious lacrimation. The vitamin C content of the urine was 0·7 mg. per cent.

Treatment with boric irrigations, gutt. atropine 1 per cent., and dry heat was carried out.

Ascorbic acid treatment was commenced immediately, and on February 19, 1941, the eye was already more comfortable and less red. By February 23, 1941, it was quiet, and the cornea almost clear, although the lacrimation and blepharospasm persisted. On March 3, 1941, the patient developed a catarrhal cold, and the eye became more irritable. The original infiltrations had disappeared entirely, but a new one developed in the pupillary area, becoming acute and breaking through the epithelium (demonstrated by staining with fluorescein). He is still under treatment with ascorbic acid, and the eye is gradually settling down. Up to the time of recording, he has received 5 grammes of ascorbic acid. His excretion of vitamin C increased after each injection.

CASE 8. Flight-Sergeant R. N. T., aged 35 years. ***Phlyctenular "ring" ulcer.*** His right eye became inflamed and painful on February 15, 1941, while he had a cold. There was no history of trauma. He was treated at his unit hospital until February 21, 1941, when he was sent in to the regional hospital.

On admission, there was intense inflammation of the conjunctiva, both bulbar and palpebral, with pronounced circum-corneal injection. The upper quarter of the cornea showed definite pannus. The remainder of the periphery was ulcerated in an unbroken line of yellowish slough about 2 mm. broad. Over the rest of the cornea

the epithelium was so oedematous and wrinkled as to be quite opaque. Pain was not a prominent feature, but there was much blepharospasm and lacrimation, and a muco-purulent discharge. A conjunctival swab showed staphylococcus albus. The vitamin C content of the urine was too small to estimate, though it increased greatly after treatment.

Local treatment was confined to irrigations with boric lotion, atropine drops and spoon bathing. 500 mg. ascorbic acid were injected intravenously every day from February 22, 1941, to March 3, 1941, and then on alternate days until March 15, 1941. In all, 7·5 grammes of ascorbic acid were given intravenously. After this treatment, tablets of ascorbic acid (250 mgms., "Roche") were administered orally at the rate of six per diem.

The condition of the cornea began to improve forty-eight hours after the first injection, and by March 1, 1941, the oedema of the epithelium and stroma had subsided sufficiently to allow the iris to be seen. This was discoloured, but the pupil was well and evenly dilated. The ulcer lost its yellow edge and commenced to heal. On March 15, 1941, the eye was quiet, and the corneal epithelium was restored except for one facet on the temporal side. On March 20, 1941, the eye was almost white, and the cornea normal except for a little flattening of the epithelium at the periphery. The pannus had almost disappeared. Their was no pain, blepharospasm, lacrimation or conjunctival discharge.

CASE 9. Aircraftsman W. J. P., aged 28 years. *Superficial punctate keratitis.* History of inflamed left eye for two months. He had been treated at his station sick quarters with boric lotion and atropine drops, with little improvement at first, but subsequently the condition gradually cleared up.

The right eye became inflamed four days ago. This was treated with boric lotion and atropine drops, but with no improvement. On admission, there was much conjunctival injection with photophobia and blepharospasm. The right cornea showed a typical superficial punctate keratitis.

Treatment was commenced with atropine drops and boric lotion. A slight improvement occurred.

On the fourth day, ascorbic acid injections were commenced, and the rapidity with which the condition cleared up was dramatic. 500 mgs. were given daily for four days, at the end of which time the eye was white. No recurrence has taken place over a period of several months.

CASE 10. Aircraftsman N. H., aged 26 years. *Generalized seborrhoeic dermatitis, with keratitis and corneal ulceration of both eyes.* History of seborrhoeic dermatitis of the scalp, commencing six weeks ago, with inflammation of the eyes for the last week. He had a diffuse seborrhoeic dermatitis of the skin, mainly involving

the scalp, face and flexures, causing much irritation. Both eyes showed superficial ulcers with vascularisation. Blepharospasm and photophobia were severe, causing bilateral spastic entropion.

He was admitted to hospital, and his eyes treated with atropine and parolein drops. The skin of his trunk and face was treated with sodium bicarbonate lotion and calamine lotion. Little improvement occurred for the first four days on this line of treatment.

The ascorbic acid clearance test was then carried out, with the following results:—

First day.—300 mgs. ascorbic acid given by mouth. Urine volume=128 c.c. during subsequent five hours. Vitamin "C" percentage=3·8 mgs. per cent.

Second day.—300 mgs. ascorbic acid given by mouth. Urine volume=107 c.c. during subsequent five hours. Vitamin "C" percentage=3·9 mgs. per cent.

Third day.—300 mgs. ascorbic acid given by mouth. Urine volume=150 c.c. during subsequent five hours. Vitamin "C" percentage=5·2 mgs. per cent.

These figures represent an initial ascorbic acid deficiency of 1,500 mgs. (Saturation is taken as corresponding with 5 mgs. per cent.)

On the following day, ascorbic acid injections were commenced, and given daily at the rate of 500 mgs. per injection for two weeks. The improvement in the eye condition after four injections was dramatic. Blepharospasm disappeared, and the corneae became much clearer.

Local treatment by means of hyoscine drops (owing to the fact that atropine irritation occurred) was continued, and at the end of two weeks the eyes had returned to normal, with the exception of two fine superficial corneal nebulae.

He is still under treatment for the skin condition, but the eyes are white and no longer irritable. Vision is 6/6 each eye.

Comments

In cases 1 to 3 there were well established infective conditions with severe corneal involvement. In each case more orthodox treatment over a considerable period proved unavailing, but after injections of ascorbic acid there was a rapid and pronounced improvement. In Case 8 the eye was in a serious condition and appeared to be threatened with imminent perforation and/or panophthalmitis. In this instance, apart from the use of ascorbic acid, treatment was reduced to a minimum. This was regarded as a stringent test of the value of vitamin C injections, and in this case cure was both rapid and strikingly complete.

Case 7 is somewhat indeterminate. The immediate result was satisfactory, but a further infiltration developed, involving the deeper layers of the corneal stroma, and this proved much more resistant.

Case 5 was a severe keratitis of somewhat unusual type, which resolved completely without any residual scarring. The disappearance of corneal opacities was also notable in Case 6, where the scars had both the history and the appearance of being of long standing. In both of these cases, as in Case 3, a similar result might have been attained by more usual methods, but in all of them recovery appeared to be greatly accelerated.

In the first three cases, which were treated tentatively and without great expectation, no attempt was made to explore the output of vitamin C. Thereafter, the vitamin C content of the urine was estimated before and after treatment for the sake of comparison. Samples were collected from 30 patients in good general health, and on full diet, and titrated with a standard solution of dichlorophenolindophenol. It was found that the average content was 0·78 milligrammes per 100 cubic centimetres of urine. Estimations made before treatment varied considerably, and appeared to have little significance. During treatment three samples were taken daily from each patient, and an appreciable increase in the amount of vitamin C excreted was taken to indicate that there was no general deficiency. The rate of excretion appeared to be highest five or six hours after an injection.

In one instance only (Case 6) was there no increase in output.

We have tried ascorbic acid in the treatment of five cases of acute iritis, but with no beneficial effect. In one instance, which was of luetic origin with a strongly positive Wassermann reaction, the condition appeared to be aggravated by the injections as the following case record shows:—

Corporal J. G. G., aged 21 years. *Acute irido-cyclitis.*—In April, 1940, he had an inflammatory condition of the right eye which proved to be irido-cyclitis. The Wassermannn reaction was strongly positive, and the condition, which was treated elsewhere by local applications and anti-luetic measures, cleared up entirely in six months.

On December 26, 1940, the left eye became slightly red and irritable. He was admitted to hospital two days later. The left eye showed a slight degree of ciliary injection, and the anterior chamber was a little deeper than normal. The right eye showed no abnormality.

Treatment with gutt. atropine was commenced, and there was no change until January 10, 1941, when the left eye began to be more irritable and showed fine deposits on the posterior corneal surface. Frequent dry heat was added to the treatment.

The condition grew rapidly worse with the formation of many K.P., some being of the mutton-fat type. There was considerable pain in the eye.

The vitamin C content of the urine was 0·9 mgms. per cent.

Treatment with ascorbic acid was begun on January 25, 1941, and injections were given at frequent intervals up to February 14, 1941, when 3·5 grammes had been administered.

During this time, the state of the eye, with some fluctuations, deteriorated steadily, and on February 19, 1941, the hyperaemia of the iris was severe enough to give rise to an hyphaema. From that date it began to settle down, the hyphaema became absorbed, and the pain was much diminished.

Two further injections of ascorbic acid were given—on March 3, and March 5, 1941. On March 7, 1941 the eye was again very irritable with a recurrence of hyphaema. No further ascorbic acid was given, and the condition is now greatly improved, although numerous fine K.P. are still to be seen. Despite a further course of N.A.B., the Wassermann reaction is still strongly positive.

Conclusions

Although there is much further work to be done on the subject, from the limited number of cases treated we think the following conclusions may be drawn:—

1. In certain corneal conditions—notably ulceration, superficial type of keratitis and chronic corneal opacities—treatment by means of ascorbic acid intravenously is of therapeutic value. The improvement in most cases is almost dramatic.

2. In most cases treated, there is no reason to believe that a general vitamin "C" deficiency exists. It appears, therefore, that the beneficial results are obtained by flooding the bloodstream with excess of ascorbic acid.

3. Ascorbic acid appears to be of no value in the treatment of iritis. It may even have a detrimental effect in certain instances.

4. The injections used (ascorbic acid "Roche" concentrated vitamin "C" ampoules, 500 mgs. per injection) caused no local or general reaction.

5. *Dosage:*—We recommend the daily injection of 500 mgs. intravenously until active inflammation of the eye has ceased, preferably followed by ascorbic acid tablets given orally (Tabs. ii t.d.s., each tablet containing 250 mgms).

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ANNOTATION

The Treatment of Burns

Recently there has been much discussion and not a little controversy in medical societies and journals about the treatment of burns. While almost all gunshot wounds are to some extent complicated by burning of the injured tissues, there are instances when the burn is caused by some special circumstances, devices or chemicals, such as the airman's burns, burns from the back-flash of large naval guns, from flame-throwers, bomb flashes, phosphorus, cordite, phosgene and mustard gas. Injuries from these sources have stimulated surgeons towards finding suitable methods of protection, such as the asbestos hood and gauntlets used by men in naval gun turrets, and in assessing the best methods of general and local treatment for burns in different parts of the body.

There is agreement about the general treatment of burns by counteracting the shock which comes on some hours after the injury. For this purpose it is necessary to apply warmth from an electric blanket; morphia grs. $\frac{1}{3}$ to $\frac{1}{2}$ repeated when necessary; the administration of plasma, at first a rapid infusion and later by the drip method until the haemoglobin concentration and the blood pressure are normal or nearly so; the administration of oxygen by the Boothby mask and cortin (supra-renal cortical hormone—desoxycorticosterone acetate) intravenously.

About the local treatment of burns there is much difference of opinion and a fair number of therapeutic agents are recommended. The two principal opponents in the controversy are those who favour the use of coagulants such as the tannic acid and silver nitrate preparations, and those who condemn these agents and trust in the application of normal saline packs and saline baths.

There is something to be said in favour of both sides depending on the degree and site of the burn. Careful diagnosis on these two points is essential for correct treatment. For instance, the application of tannic acid preparations to burns of the eyelids renders these important protective structures rigid and contracted, endangering the eye from exposure and rendering any ocular treatment that may be necessary impossible to perform satisfactorily, or even at all. Yet during the past year the eyelids of burnt airmen have been tanned with disastrous results to vision. The use of this agent in third degree burns leads to a dense adherent coagulum, intense oedema of adjacent tissues, and later infection, thus increasing fibrosis and contracture deformity. Some authorities consider that the use of tannic acid on the hands leads to digital necrosis, particularly over the site of joints, and produces rigid spindle-shaped useless fingers.

The treatment by saline packs and baths requires constant attention, good team work and nursing and absolute asepsis. It is interesting to note that burnt sailors during immersion in the sea experience no appreciable pain. This is also the case when saline baths are administered, particularly by such an ingenious method as the Bunyan-Stannard waterproof silk-cloth envelopes, applicable to the limbs and trunk. For facial burns a gauze mask with apertures for the eyes, nose and mouth is kept continually soaked by a saline drip apparatus, drainage being effected by a jaconette collar. The advocates of this method of treatment maintain that mobility of the tissues is encouraged in the saline bath. When healthy granulations appear and are just below the level of the epidermis, skin grafting is carried out. In clean early cases when the burn is not a deep third degree type, a Thiersch or split skin graft is the best dressing after surgical toilet of the injured area. Pain is immediately relieved and the functional result is generally good.

Tulle gras, a dressing consisting of a 2 mm. mesh impregnated with soft paraffin, balsam of Peru and halibut oil, is valuable for covering the burnt surface and preventing the saline packs from adhering to the tissues.

One authority maintains that saline causes severe maceration and irritation of the tissues and that instead sod. hypochlorite 2·5 per cent. should be used combined with normal saline.

Acriflavine in cod liver oil has been advocated for face burns but condemned by one critic as rapidly producing infection. Some surgeons advise the immobilization of burnt limbs in plaster of Paris for the relief of pain, others think that this encourages stiff joints.

Certain chemicals are suggested for certain types of burns, for instance, copper sulphate 2 per cent. for phosphorus, sodium bicarbonate for cordite, phosgene and mustard gas burns together with bleach for the latter.

In these published discussions the voice of the eye surgeon appears neither to have been raised in recommendation nor in protest. The truth is that at present there is need for thorough and critical clinical investigation comparing the efficacy of various therapeutic agents in different types of burn. In burns affecting the eyelids, particularly in airmen, the lid margins generally escape injury. It would seem that early tarsorrhaphy and Thiersch grafting in such cases may have an important place in treatment, Of the coagulants, tannic acid preparations should be condemned as dangerous. Sodium nitrate 10 per cent. preceded by the application of gentian violet 1 per cent. or triple dye (Aq. gentian violet 2 per cent., brilliant green 1 per cent., acriflavine 0·1 per cent.), justifies a trial in first and second degree burns after preliminary tarsorrhaphy. Saline packs moistened by a continuous drip

apparatus will require the most constant nursing supervision and strict asepsis. A comparison of the results of early and late skin grafts will be interesting, as also the results of the sulphonamides applied locally and administered by the mouth.

ABSTRACTS

MISCELLANEOUS

(1) **Metivier, V. M. (Trinidad).—Intra-ocular foreign bodies in Trinidad and Tobago.** *Carribean Med. Jl.*, Vol. II, No. 3, 1940.

(1) **Metivier** reviews his cases of intra-ocular foreign bodies between May, 1932 and May, 1940. In this period 32 patients out of a total of 14,940 new cases had intra-ocular foreign bodies. This incidence is rather higher than the 1 per 1,000 cases in records from Manchester, Wolverhampton and Moorfields.

A Haab giant magnet was procured for the Colony in August, 1934. Before this seven cases had come in in 1932, and one case in 1933. Some of these had to travel to Europe for attention.

Of the author's cases 30 were cases of magnetic foreign bodies. The visual results in 20 cases are given and they were good or very good in 50 per cent. of the patients. The rôle of occupation as the causation factor is shown; and the number of cases among persons employed in local industry is relatively smaller than would be expected. "Apart from the manufacture of sugar and the production and refining of mineral oil and its by-products, major works of importance in the period under review were the construction of the new deep water harbour and the central water supply scheme." The cases from private and hospital practice are shown in tabular form as well as the visual results and a classification of all magnetic foreign bodies, in respect of occupational risk.

R. R. J.

(2) **Blumenthal, C. J. (Johannesburg).—Simple detachment of the retina. A review of sixty-eight operated cases.** *South African Med. Jl.*, August 24, 1940.

(2) **Blumenthal** reviews the clinical facts about 68 patients who underwent operation for simple detachment of the retina. He stresses the importance of very careful pre-operative examination, a thorough study being made of the entire fundus. In spite of an obvious retinal hole or tear it is surprisingly frequent to find a fine split or small hole at another site which if unrecognized would lead to operative failure.

The author comments on the loss of corneal transparency under instillation anaesthesia of cocaine or pantocain, and instead recommends injections of novocain into the lids so that the palpebral conjunctiva is anaesthetized and also retrobulbar injection into the region of the ciliary ganglion.

He emphasizes the importance of inducing a coagulation effect in the retina, visible with the ophthalmoscope, around the site of the hole by the application of surgical diathermy. When the retina is ballooned forwards by a collection of inter-retinal fluid 4 mm. or more deep, this coagulation is difficult or impossible to effect and in such cases the author recommends the withdrawal of the fluid by oblique transfixation of the sclera and choroid with a fine hollow ground needle and aspiration.

The author believes that the position of the patient in bed after operation makes little difference to the result provided he is comfortable. He condemns the use of aperients and describes a case where a dose of salts induced prolapse of haemorrhoids and resulted in restlessness. He considers that retinal detachments are best nursed in a ward by themselves and without the disturbing effect of ambulatory cases around them.

The results of operation are set out in tables grouped according to the nature of the retinal detachment or hole.

H. B. STALLARD.

(3) **Boshoff, P. H. and Rethmeier, B. J. (Leyden).—The Roentgenological examination of the optic nerve.** *Ophthalmologica*, Vol. XCIX, p. 378, 1940.

(3) **Boshoff** and **Rethmeier** in a preliminary report on the use of per-abrodil and its isotonic solution for demonstrating the optic nerve, gave details of its use by retrobulbar injection in five patients. After an injection Roentgenograms were made every five minutes and the optic nerve was photographed in diameter and in length.

In two anophthalmic orbits the nerve was demonstrated in cross section after ten minutes, by the formation of a ring of contrast probably indicating the peri-dural space of the nerve. In a patient with siderosis bulbi, the nerve was to be seen as a diffusion defect in a uniform contrast shadow behind the globe. After some time the contrast shadow became thinner around the nerve, while the peri-dural contrast ring remained. From this they concluded that the main resorption takes place around the nerve. This fact constitutes the physiological basis for this investigation.

In two cases it was possible to see in its entire length that part of the optic nerve which is immediately behind the globe. In two other cases the absence of the normal shadow of the nerve was an indication of a pathological condition.

ARNOLD SORSBY.

BOOK NOTICES

A Treatise on Medico-legal Ophthalmology. By ALBERT C. SNELL, M.D. Royal 8vo, pp. 312, with 15 illustrations. London: Henry Kimpton. 1940. Price, 30/- net.

Not since 1902 has any complete treatise on visual economics been published in English, though Würdemann, in the second edition of his "Injuries of the Eye," devoted three chapters to medico-legal ophthalmology. Dr. Snell has been making contributions to this subject for nearly 30 years and has now brought out a complete work on the subject which does him great credit.

The book is arranged in three sections: the first of these discusses some essential principles of medical jurisprudence and an analysis of compensation laws as these relate to visual disabilities. Section two deals with the evaluation of visual disabilities and the determination of fractional parts of vision. Section three discusses the practical application of the visual efficiency computation to medico-legal practice. There is also an appendix containing excerpts from court decisions and the Longshoremen's and Harbour Workers' Compensation Act in the District of Columbia, which Snell states "forms a nearly perfect ideal as a basis for determining visual disabilities and for awarding compensation."

We have to remember that there is no complete uniformity in the Statutes of the various States of the U.S.A.

The Courts place a broad interpretation on the term injury, they do not consider it entirely synonymous with trauma. "For example, retinal detachment may be compensated under the interpretation of injury when it is not specifically classed among industrial eye diseases." Two cases are briefly related to illustrate this point.

"There is no logical ground for any compensation law to specify that the loss of vision shall be determined without the aid of glasses, and it is unwise to make any compromise about their use in estimating the visual loss after an eye injury. The Statutes of all States should specify, as the majority do, that visual efficiency shall always be determined with the use of corrective glasses."

Acuity notations are not fractional parts of vision as Snellen was careful to point out. They "definitely measure the size of the visual angle and clearly express in the form of a ratio the size of the observed angle compared with the normal."

The chapter on the percentage evaluation of visual perception is masterly. The problem is approached mathematically and tables and graphs show the results reached. Table VI is as follows:—

			per cent.		per cent.		
20/40	corresponds to	about	$83\frac{1}{3}$	vision or	$16\frac{2}{3}$	loss of	vision.
20/65	,,	,,	$66\frac{2}{3}$	,,	$33\frac{1}{3}$	,,	,,
20/100	,,	,,	50	,,	50	,,	,,
20/150	,,	,,	$33\frac{1}{3}$	,,	$66\frac{2}{3}$	,,	,,
20/250	,,	,,	$16\frac{2}{3}$	,,	$83\frac{1}{3}$	,,	,,

The chapter on peripheral vision and its evaluation is also very good as are those on the examination of injured eyes and on malingering.

We congratulate Dr. Snell on having written a most valuable book in a truly scientific manner and feel that it can be commended not only to all practising ophthalmic surgeons but also to members of the legal profession. It is likely long to remain a classic in its own line.

Paper and printing are very good, and there is a complete index.

Practical Orthoptics in the Treatment of Squint. By KEITH LYLE, M.D., M.CH., M.R.C.P., F.R.C.S., and S. JACKSON (Orthoptist). Second Edition. Pp. 356, illustrations 101 (including 5 plates). London: H. K. Lewis and Co., Ltd. Price, 15s. net.

The second edition of this book has been enlarged and brought up to date. In chapter III, dealing with the aetiology of strabismus, the views of Bernard Chavasse expressed in his recently published book, "Worth's Squint," have been incorporated. In the chapter about instruments, a description of Group-Captain Livingston's rotating stereogram has been inserted.

The authors have added a new chapter on adult cases of squint and the chapters on paralytic squint and ocular torticollis have been enlarged by additional matter.

In classifying the results of treatment the authors have adopted the "standard of cure" approved by the Orthoptic Board.

A statement in connection with evipan anaesthesia to the effect that if a period of anaesthesia longer than 20 minutes is required, a second injection of evipan may be given at the end of that period is open to criticism from anaesthetists who prefer to keep the needle in the vein and graduate the dose as necessity arises after the initial "knock out" dose of 0·3 gm. has been administered rapidly in 10-15 seconds. Incidently some consider that sodium pentothal should supersede evipan for it causes no muscular twitchings, produces greater muscular relaxation and more peaceful anaesthesia.

At the end of the book is an analysis of 511 patients treated in the orthoptic department of the Royal Westminster Ophthalmic Hospital during 1938. The figures are of interest in giving the incidence of the different types of squint and heterophoria, the length of treatment required, and the result to be expected.

This book is written in an interesting and lucid manner, it is admirably illustrated, and its subject is of considerable importance to ophthalmic practitioners.

Transactions of the American Ophthalmological Society. Vol. XXXVIII. Philadelphia. 1940.

The seventy-sixth annual meeting of the American Ophthalmological Society was held at Hot Springs, Virginia, on June 3, 4 and 5, 1940, under the presidency of Dr. E. V. L. Brown. The Transactions contain many papers of considerable medical, surgical and pathological interest, and some of these we hope to notice as abstracts. The standard of these papers is high and many of them are admirably illustrated. Of particular current interest to those of us engaged in traumatic surgery is the paper reporting a demonstration of fracture of the orbit by planigraphy. By routine X-ray methods linear fractures of the orbit are especially difficult to detect. The paper on the sterilization of sharp instruments by chemical solutions is important. There is one paper about sulphanilamide therapy for inclusion conjunctivitis.

The Transactions also contain reports from sub-committees dealing with such matters as prizes, physical therapy, ophthalmic history, trachoma and orthoptic training. The finances of the Society appear to be very satisfactory. The production of the Transactions is up to its usual high standard.

Essentials of General Anaesthesia. By R. R. MACINTOSH, M.A., M.D., F.R.C.S., D.A. and FREDA B. PRATT, M.D., D.A. Pp. 324, illustrations 226 (some in colour). Oxford: Blackwell, Ltd. Price, 25s.

This book is written with special reference to dental surgery, a field in which the care of the unconscious patient and the exercise of considerable judgment in the administration of appropriate anaesthetics demands a degree of skill and sound technique which affords the basis for anaesthetic work in other fields of surgery.

There are interesting chapters on the history of anaesthesia; the theory of anaesthesia; respiration and cyanosis. The illustrations, many of which are coloured, are clear and admirably produced. The section dealing with the intravenous administration of barbiturates such as pentothal sodium will interest eye surgeons now that this drug is used for eye operations lasting about 20 minutes, or less than this time. The proper administration of general anaesthesia through the devices used in dental surgery is not without application to the opening of acute abscesses in the eyelids.

This book is well written. It is easy and enjoyable to read. The production is good.

NOTES

Death

THE death of Dr. Emory Hill, of Richmond, Virginia, is announced in the February issue of the *American Journal of Ophthalmology* and from its obituary notice we extract the main points. Dr. Hill came of old Virginian stock and was born in 1883. After graduating B.A. at Columbia University he began his professional education at the Medical College of Virginia, and at the same time did some teaching of English. From Virginia he went to Philadelphia where he came under the influence of Weir Mitchell and de Schweinitz among others. Hill began the practice of ophthalmology at Chicago, and later returned to Richmond, Virginia, where for the past ten years he had been Professor of Ophthalmology. From 1925 to 1932 he was Secretary of the American Ophthalmological Society.

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Graduate Study in Ophthalmology

NEW York University, under the direction of Professor Berens, offers a comprehensive three-year full time course in ophthalmology. Pre-requisites for admission are based on general university requirements. In the first year lectures and laboratory work on a large variety of subjects are outlined. The last two years comprise an internship during which the candidate is required to investigate some problem and report on the results of his research. There are three residences in the ophthalmological service of the Bellevue Hospital for which students may apply. Besides this a residency can be taken at institutions approved by New York University, which are practically those approved by the American Medical Association and the and the American Board of Ophthalmology.

The first year's work may be taken without a subsequent internship or residency, but such a course does not lead to a degree. The tuition fee for one year of full-time work is 400 dollars. There is a yearly registration fee of 12 dollars for the subsequent years of clinical work, but no further tuition fee. Students with an exceptional record may, on the recommendation of the committee on Graduate Medical Education, become candidates for the advanced degree of Doctor of Medical Science. The conditions for this degree are outlined and further information, together with the full syllabus of lectures and lecturers may be obtained from Prof. Daniel B. Kirby, at the office of the Assistant Dean, College of Medicine, New York University, 477, First Avenue, New York.

Study of the subjects of lectures together with the names of lecturers and the number of hours given for each subject show that this course is really comprehensive, numbering 34 subjects. The number of hours vary from 188 in refraction, 128 in gross anatomy and 136 in histo-pathology to 8 in perimetry, with an added 4 in technique and 2 each in telescopic and contact lenses and gonioscopy.

Honours Mr. T. Harrison Butler has been elected F.R.C.S. (Eng.) as a member of twenty years' standing. Mr. R. R. James has been elected a corresponding member of the American Association of the History of Medicine.

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Corrigendum In Mr. Nigel Cridland's paper (Part II) on page 189 last line but seven, "truth" should have been printed "Truth." On page 210, Table IV, the letters "RG" should appear above "MR," and in line with the upper of the two rows of figures in the table.

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CLINICAL NOTE

The Prevention and Treatment of Infection in Wounds by Sulphonamides. (Brochure published, 1941, by MAY and BAKER.)

The sulphonamides have a bacteriostatic action on certain organisms at a concentration which does not affect leucocytes or other natural defence mechanism. They are feeble antiseptics and are not harmful to the skin and mucous membranes.

Experimental and clinical work shows that the application of sulphanilamides to wounds, other than those involving the central nervous system, does not cause irritation and delays the development of streptococcal infection. Local application has taken the form of dusting the wound with powdered sulphanilamide 5-15 grm. Some authorities are in favour of using a thick suspension by adding 2 grms of powdered sulphanilamide to 100 c.c. of 0·8 per cent. solution of sulphanilamide in physiological saline solution.

The packing of wounds with gauze soaked in a saturated aqueous solution of a very sparingly soluble compound such as sulphapyridine or the rather more soluble sulphanilamide is ineffective as the concentration reached in the adjacent tissues is quite insufficient for any bacteriostasis.

In 2 to 4 days the drug disappears from the wound and also the blood stream so that it will not give protection against late infection. It is therefore as well to follow up the local application of sulphanilamide to the wound with oral administration starting on the 2nd or 3rd day.

Anaerobic streptococci are not susceptible to the action of the sulphanamides. It seems from experimental work that sulphapyridine has a greater bacteriostatic action than sulphanilamide. In the treatment of gas gangrene adequate control will only be secured in most cases when chemo-therapy is combined with the administration of antitoxin.

In wounds of the brain and nerve tissue, dusting with one of the sulphanamide preparations evokes foreign body irritation. It seems preferable to use the drug in solution. If, however, a powder must be employed it should be used sparingly. Sulphanilamide is better than sulphapyridine.

Experimental work suggests that the tensile strength of healed wounds seems to be greater after oral sulphanilamide therapy than when it is not used, but histologically there is little difference between the wounds so treated and the controls.

The implantation of the sulphonamides in heavily infected tissues is of little or no value. In such cases it seems that the large numbers of bacteria, peptones and bacterial extracts inhibit their bacteriostatic action, and sloughs, necrotic tissue and interference with the local blood supply render adequate absorption of the drug ineffective.

If the sulphonamide powders are contaminated by organisms or their spores the bacteriostatic action of the drug should render sterilization unnecessary.

However, sulphonamide powder, moistened with water, may be sterilized by filling ampoules which are then sealed and autoclaved at 10 lbs. pressure at a temperature of approximately 115°C. If dry instead of moist heat is used at a temperature of 150° C. it should be maintained for one hour.